CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-115s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22115
Submission Code	BZ
Letter Date	8/27/08
Stamp Date	8/28/08
PDUFA Goal Date	5/31/09 (after 3 month extension)
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	5/3/09
Established Name	lamotrigine extended-release
(Proposed) Trade Name	Lamictal XR
Therapeutic Class	Anticonvulsant
Applicant	Glaxo Smith Kline (GSK) Pharmaceutical Co
Priority Designation	S
Formulation	Extended-release
Dosing Regimen	Once daily
Indication	Adjunctive Treatment of Partial Epilepsy
Intended Population	Patients $\geq$ 13 years old

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- I recommend that XR lamotrigine be approved as safe and effective adjunctive treatment of partial seizures in adults (ages $\geq$ 17 years).

1.2 Recommendation on Postmarketing Actions

- I recommend that the sponsor conduct a Phase 4 pharmacokinetic study in adolescents (13-16 years) to determine and confirm that lamotrigine exposure is similar to that for adults for XR lamotrigine treatment. If this similarity is confirmed, one could dose adolescents with same dosing regimen as that used for adults. If the exposure is not similar, then the sponsor would need to conduct a randomized, double-blind, placebo-controlled study in adolescents (13-16 years) to determine the efficacy and safety of XR lamotrigine treatment.

I make this recommendation because I cannot conclude that there are adequate pharmacokinetic, efficacy, and safety data to approve XR lamotrigine treatment for this population of pediatric patients.

- I recommend that the sponsor conduct a Phase 4 study to characterize the dose/exposure-response curve for efficacy and safety for XR lamotrigine.

I make this recommendation because the sponsor has not characterized the dose/exposure - response curve for efficacy and safety for XR lamotrigine nor for the immediate-release formulation of lamotrigine. Such characterization would be desirable considering : 1) the complexity of dosing for either formulation of lamotrigine based upon concomitant AEDs; 2) that different serum lamotrigine levels are achieved with different dosing regimens depending on concomitant AEDs; 3) that it is not unequivocally clear if there is increased therapeutic benefit from increased lamotrigine exposure; 4) that patients could be exposed to increased, unnecessary safety risks if they are exposed to increased lamotrigine exposure without the opportunity for increased therapeutic benefit.

It may be desirable to conduct this phase 4 study in patients using “neutral” concomitant AEDs by randomizing patients to placebo or one of at least 3 different concentration ranges of lamotrigine (i.e., “low,” “intermediate,” and “high”). If a concentration/exposure-response was demonstrated, then dosing with various concomitant AED regiments could be recommended based upon concentrations achieved with the various regimens. Results obtained with treatment with XR lamotrigine could be extrapolated to treatment with the immediate-release formulation of lamotrigine.

1.2.1 Risk Management Activity

- A Medication Guide will be issued.

1.2.2 Required Phase 4 Commitments

- I recommend that the sponsor be required to conduct a phase 4 study to characterize the concentration-exposure response and determine what is optimal dosing for XR lamotrigine (see 1.2 of Executive Summary). Results would also be applicable toward recommending optimal dosing for the immediate-release formulations of lamotrigine.

1.2.3 Other Phase 4 Requests

- Not applicable

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lamotrigine extended-release (XR lamotrigine) is a new, enteric coated, formulation for a once daily dosing regimen. The clinical development program for XR lamotrigine consists primarily of seven Phase I Clinical Pharmacology studies conducted in healthy volunteers (LAM10007, LAM10004, LAM10005, LAM100014, LAM100017, LAM105537 and LAM102611). In addition, one important short-term study (LEP103944) conducted in patients with epilepsy evaluated the pharmacokinetics and safety experience of patients who were converted from immediate release (IR) lamotrigine to XR lamotrigine and then back to IR lamotrigine. The main clinical pharmacology studies mainly evaluated the single and multiple dose pharmacokinetics, dose proportionality, dosage strength equivalency, food effect and the conversion from the immediate release dosage form to the proposed extended release dosage form and a drug interaction study with esomeprazole. The other studies were exploratory and formulation development in nature.

In addition to these studies, blood samples for population pharmacokinetic (PK) analysis were collected in one pivotal, (Phase III) randomized, double-blind, placebo-controlled Clinical Study evaluating the efficacy and safety of XR lamotrigine as adjunctive treatment for partial seizures in patients 13 years of age and older (LAM100034). The study population consisted predominantly of patients taking concomitant valproic acid (VPA) or enzyme-inducing anti-epileptic drugs (EIAEDs) or “neutral” AEDs (AEDs that do not alter plasma lamotrigine levels). A thorough QTc study was also conducted using the IR dosage from.

1.3.2 Efficacy

The efficacy of XR lamotrigine was established in a single, pivotal, randomized, double-blind, placebo-controlled study (LAM100034; also known as Study 34) that involved a 19 week study

(including a 7 dose escalation period and a 12 week maintenance period) in which patients were randomized to placebo or XR lamotrigine. Patients were randomized to a different, targeted daily dose of XR lamotrigine depending one of three concomitant anti-epileptic drug (AED) categories (1. VPA or VPA with other concomitant AEDs; 2. "other" AEDs that do not alter serum lamotrigine levels; 3) enzyme-inducing AEDs).

The following schematic diagram outlines the study design for Study 34.

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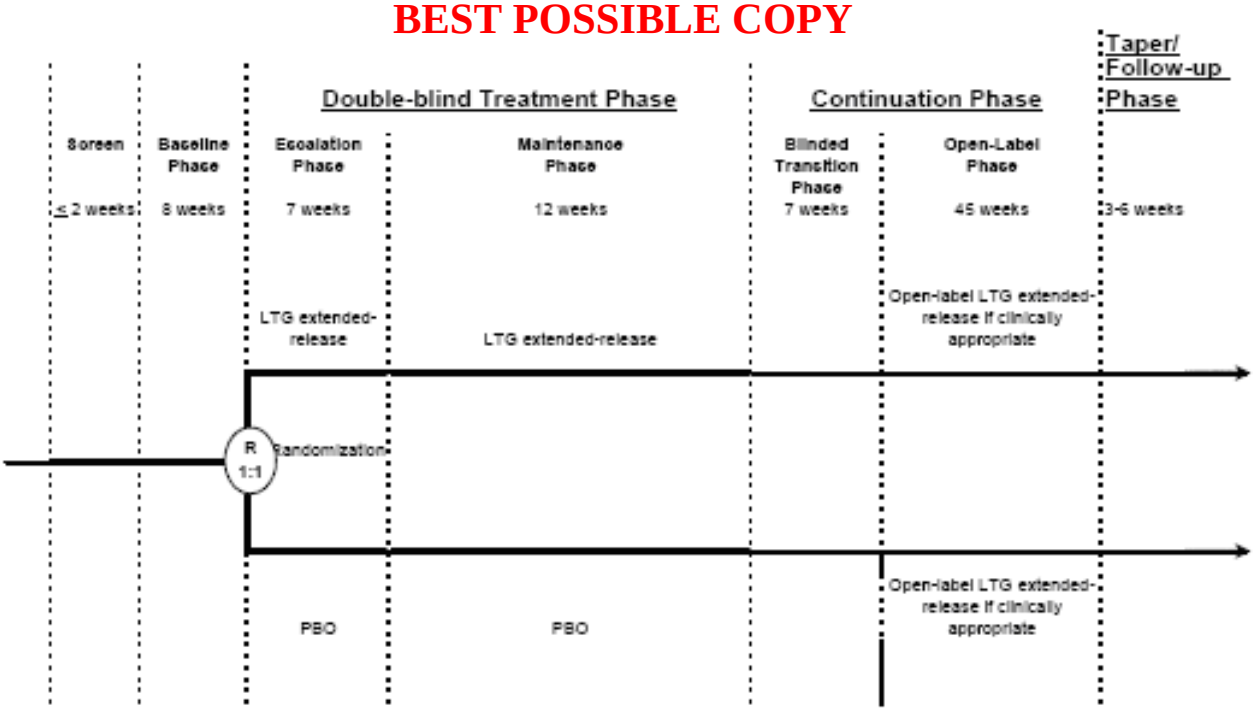


Overall. XR lamotrigine was statistically superior to placebo ($p < 0.0001$) in all patients in the modified Intent-to-Treat (ITT), primary analysis of the primary efficacy endpoint, median the percentage reduction in seizure rate from baseline over the whole study period. The median percent reduction in weekly seizures was 47 % for XR lamotrigine and 25 % for placebo. The estimated treatment difference (based upon the Hodges Lehman estimates for the median treatment difference, 95 % confidence interval, and p-value are based upon the Wilcoxon Rank Sum test) was 19.2 and the 95 % confidence interval (CI) for the difference was 9.5 and 28.8.

At the time of the original review, there was a concern about the efficacy of XR lamotrigine in U.S. patients, who accounted for nearly 40 % of the randomized patients, compared to the clear efficacy demonstrated in non-U.S. patients, who were studied predominantly in countries for which the DNP does not have much experience. The sponsor has addressed possible reason for this concern expressed by the DNP. This review outlines and discusses possible explanations for this discrepancy. Part of the reason for this discrepancy may have been related to a larger disproportionate percentage of foreign (non-U.S.) patients who were treated with VPA and

achieved somewhat higher lamotrigine concentrations. However, the main reason for this discrepancy may be related to a much larger placebo "response" in U.S. patients.

1.3.3 Safety

The safety of XR lamotrigine was demonstrated in the sponsor's clinical development program. The safety profile for XR lamotrigine is generally considered to be relatively similar to that characterized for the immediate-release formulation of lamotrigine.

1.3.4 Dosing Regimen and Administration

The recommended dosing regimen and administration is primarily based upon the dosing regimen outlined in the protocol for study 34 and the experience of patients who were treated in this study.

The following table outlines my dosing recommendations for XR lamotrigine.

Table 1. Escalation Regimen for LAMICTAL XR in Patients ≥ 17 Years of Age

	For Patients TAKING Valproate	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate. Rifampin or Estrogen-containing oral contraceptive preparations	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin or Estrogen-containing oral contraceptive preparations and NOT TAKING Valproate
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance Range (Week 8 and onward)	200-250 mg every day #	300-400 mg every day #	400-600 mg every day #

Dose increments at week 8 or later should not exceed 100 mg daily at weekly intervals.

1.3.5 Drug-Drug Interactions

There are many known drug-drug interactions for the immediate-release formulation of lamotrigine. No new, significant drug-drug interactions were identified in the clinical

development program for XR lamotrigine. See Clinical Pharmacology review for additional details.

1.3.6 Special Populations

Although the sponsor studied relatively few pediatric patients (13 -16 years old) in pivotal study 34, I am unable to conclude that adequate or sufficient pharmacokinetic (PK) , efficacy, and safety data were collected to recommend approval of XR for adolescent pediatric patients aged 13-16 years. My concerns about the pediatric, adolescent data are outlined in section 5

2. INTRODUCTION AND BACKGROUND

This review relates to the sponsor's Complete Response to an Agency Approvable letter issues for NDA 22115 for XR lamotrigine for adjunctive treatment of partial seizures. The original NDA was submitted on 11/22/06. Several issues were identified in the Approvable letter as requiring responses from the sponsor. These issues are described in section 4, Submission Containing Sponsor Responses to FDA Requests.

3. RESULTS OF DSI INSPECTIONS

The following represents a summary of the inspection results from DSI.

I. BACKGROUND:
GlaxoSmithKline received an approvable letter for NDA 22-115 on September 21, 2007, requesting that the sponsor re-evaluate data obtained from foreign sites participating in LAM100034. As a result, the sponsor reported that it conducted a comprehensive data verification audit on all subjects at all study sites and reported their findings to the Agency. The sponsor has resubmitted a drug application after representing that the sponsor audited all of the sites relative to efficacy, safety, and exposure data.

The review division requested inspection of protocol LAM100034: "A multi-center, double-blind, randomized, parallel group, evaluation of Lamictal extended-release (LTG XR) adjunctive therapy in subjects with partial seizures. The sponsor resubmitted results from protocol LAM100034 in support of NDA 22-115.

The primary objective of study protocol LAM100034 was to assess the efficacy of once daily adjunctive therapy with LTG extended release in subjects with partial seizures. The primary endpoint was to determine the percent change from baseline in partial seizure frequency during the entire double-blind treatment phase (week 19).

The inspection targeted four foreign clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Gagik Avakian, M.D. Neurological Neurosurgery Department RGMU, Leninskiy Pr., 8 Moscow Russian Federation 117049 Site 079166/021276	Protocol LAM100034 7 subjects	11/10-11/08	Pending (Preliminary classification NAI)
Elena Belousova, M.D. Moscow Pediatrics and Children Surgery Institute Str., Moscow Russian Federation125412 Site 079171/021281	Protocol LAM100034 6 subjects	11/12-13/08	Pending (Preliminary classification NAI)
Sergev Gromov, M.D. St. Petersburg Research Psychneurological Institute Named after Bekhterev, Bekhtereva str.3 St. Petersburg, Russian Federation 193019 Site 079168/012278	Protocol LAM10034 5 subjects	11/17-18/08	Pending(preliminary classification NAI)

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Nadezhda Korolova.M.D. Human Brain Institute, 9 Academician Pavlov str. St. Petersburg, Russian Federation 19376 Site 079165/021275	Protocol LAM100034 8 subjects	11/19-20/08	Pending (preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol LAM100034
1. Gagik Avakian, M.D.
Moscow
Russian Federation

At this site, a total of 7 subjects were screened; 7 subjects were randomized and 7 subjects completed the study. Six subjects rolled over into the open-label phase of the study, and one subject refused to enter the open label phase due to gastric pain. Informed consent for all subjects was verified. The medical records for all subjects' files were reviewed including drug accountability, concomitant medication, diaries, laboratory results and adverse events. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

The medical records/source data for all subjects were reviewed in depth, and the source data were compared to case report forms and data listings for primary and secondary efficacy endpoints. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Elena Belousova, M.D.
Moscow
Russian Federation

At this site, a total of 7 subjects were screened; one subject was reported as screen failure, 6 subjects enrolled and completed the study. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, and source documents were compared to data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events.

Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

3. Sergev Gromov, M.D
St. Petersburg
Russian Federation

At this site, a total of 6 subjects were screened; one subject was reported as screen failure. Five subjects were randomized; 3 subjects completed the study, and one subject entered the open label. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, concomitant medications, laboratory results, diaries and source documents were compared to data listings for primary efficacy endpoints and adverse events. Subject 2095 withdrew from the study due to adverse events (tremor and weakness). Subject 2094 died unexpectedly and the cause of death was not known to the FDA team during the inspection. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

4. Nadezhda Korolova, M.D.
St. Petersburg
Russian Federation

At this site, a total of 9 subjects were screened; one subject was reported as screen failure; two subjects withdrew consent; 8 subjects were randomized (2 received LTG and 6 received placebo) and six completed the study and entered the open-label phase of the study. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, concomitant medication, laboratory results, diaries and source documents were compared to data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS
The inspection of Drs. Avakian, Belousova, Gromov and Korolova revealed no significant problems that would adversely impact data acceptability. The EIRs for these inspections essentially reflect the information in this consult. currently pending. The data submitted from the inspected sites are acceptable in support of the pending application.
{See appended electronic signature page}
Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations
CONCURRENCE:
{See appended electronic signature page}
Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

Reviewer Comment :

- There did not appear to be any significant concerns raised as a result of DSI inspections in 4 additional sites in Russia. After receipt of the problems of efficacy and safety data collected at the 2 Korean sites in 2007, there were serious concerns about poor quality of data collected for the pivotal study (#34). However, results of these inspections did not suggest a reason for serious concern about the quality of data collected in these sites and perhaps many other global sites.

- **There is one important point of information to note as one reads through this review. In some instances the sponsor has referred to the category of concomitant AEDs as "VPA alone." However, this categorization is not completely accurate because patients in the "VPA alone" category could either be taking VPA alone or VPA with another "neutral" AED that does not alter lamotrigine levels.**

4. SUBMISSION CONTAINING SPONSOR RESPONSES TO FDA REQUESTS

RESPONSES TO APPROVABLE LETTER ISSUES

GlaxoSmithKline (GSK) is providing responses to FDA requests relative to **NDA 22-115** that were received from FDA in the Approvable Letter (dated **September 21, 2007**). Comments from the FDA review team are in italics followed by the response from GSK in plain text.

SPONSOR'S EXECUTIVE SUMMARY OF ITS RESPONSE

A comprehensive response to the **Approvable Letter** is provided in this document. The Agency raised questions regarding an apparent difference in efficacy between U.S. and non-U.S. regions and the integrity of data from countries and regions with which the Agency had only limited experience.

• As requested, an exposure- response analysis has been carried out focusing on U.S. vs non-U.S. regions. This analysis did not show any difference in exposure-response between U.S. and non-U.S. regions. (**Section 1.1.2**, Exposure-Response Analyses).

• The apparent difference in efficacy between the U.S. and non-U.S. regions has been examined in detail. This analysis revealed a higher prevalence of use of concomitant valproic acid (VPA) in the non-U.S. regions that provided an important contribution to the difference in efficacy. This difference is based on an earlier onset of efficacy in patients taking concomitant VPA at least in part related to the higher lamotrigine concentrations achieved and maintained in these patients. (**Section 1.1.1**, Regional Differences in Efficacy).

• GSK has conducted a comprehensive data verification audit of all sites and patients (US and non-US) involved in the efficacy study **LAM100034**. This audit resulted in a limited number of changes to the original database which did not alter the initial assessment of efficacy and safety in study **LAM100034**, as submitted to the Agency in **November 2006**. In this submission, the processes involved in routine monitoring, auditing practices, and the comprehensive data verification audits are provided, together with summaries of the changes that were identified. (**Section 1.2**, Study Conduct).

These comprehensive data verification audits and data analyses have confirmed the reliability of data from all sites (US and non US) and verified the robust efficacy, safety and PK findings presented in the original **NDA 22-115**.

Reviewer Comment :

- This reviewer will comment when appropriate within the each of the following Sponsor's Summary sections for items that the DNP asked the sponsor to address in the Approvable

letter. I will also provide additional comment when appropriate relative to a specific document or data related to issues of concern noted in the Approvable letter.

CLINICAL
Additional Data Analyses

Regional Differences in Efficacy

FDA Comment:
"Although we acknowledge that the results of Study LAM100034 (hereafter referred to as Study 34) clearly reach statistical significance overall, we are concerned about the marked discrepancy between the results in the U.S. and non-U.S. centers. Specifically, the median percentage change from baseline in seizure frequency (i.e. primary efficacy endpoint) for XR lamotrigine in foreign sites is 50% vs 23% for placebo and the median percentage change from baseline in seizure frequency for XR lamotrigine in U.S. sites is 37% vs 33% for placebo. The median treatment difference (according to the statistical analysis) was % in the U.S. (p = 0.68) and 26% in foreign sites (p < 0.0001), and the estimate of the treatment difference in the U.S. is substantially smaller than in any other foreign country. Considering that approximately 36% of randomized patients were studied in the U.S. (more than in any other foreign country), this difference is clearly not related to an inadequate sample size. We have attempted to discover an explanation for this major discrepancy in effect of XR lamotrigine and to identify alternate analyses that might shed light on this difference. We have been unable to accomplish either.
For example, we have examined whether or not the imbalances in background AEDs between U.S. and non-U.S. patients (e.g., 9% of U.S. patients had regimens including valproate compared to 35% of non-U.S. patients; 57% of U.S. patients had regimens with EIAEDs without valproate compared to 47% of non-U.S. patients) might have resulted in a systematic decrease in lamotrigine levels in U.S. patients compared to non-U.S. patients. However, despite these differences, it appears that there is considerable overlap in the plasma levels of U.S. and non-U.S. patients.
Nonetheless, you might be able to pursue this approach further (in this regard, we note that 33% of U.S. patients had "other" AED regimens compared to 18% of non-U.S. patients; perhaps it might be worthwhile pursuing this observation)."

GSK Summary Response:
The apparent regional differences in efficacy observed in study **LAM100034** have been investigated further and are discussed in the U.S. versus Non-U.S. Analysis Document**.** This analysis revealed a greater use of concomitant valproic acid (VPA) in non-U.S. regions that largely accounted for the apparent regional differences in efficacy.

Reviewer Comment :

- The sponsor has noted here that it believes that a disproportionately greater use of VPA in non-US sites compared to US sites largely accounted for the striking "regional" difference in efficacy. Although I believe that this may have been a contributory factor to the large difference in efficacy, I disagree that this explanatory observation "largely accounted for the apparent regional differences in efficacy." I believe that perhaps the greatest factor contributing to the difference was the relatively much larger placebo "response" in US

patients for the primary efficacy endpoint vs the much lower placebo "response" exhibited by non-US patients. In this sponsor summary document, the sponsor did not point out that the different placebo responses played much of a possible explanation for the different efficacy results. However, the sponsor did suggest a more significant potential contributory role of the difference in placebo results for US vs non-US patients in the sponsor's separate document (U.S. versus Non-U.S. Analysis Document) addressing possible reasons for the regional difference in efficacy. My review will subsequently present the sponsor's argument in more depth later in this review and I will provide more detailed comments relative to this document later in this review. Analyses of subgroups of patients on various concomitant AED regimens excluding VPA (presented later) showing that efficacy was still much better in non-US patients (vs US patients) will further support my contention that a disproportionate use of VPA was not a major factor (or at least not the most important factor) explaining the regional difference in efficacy.

GSK Specific Response :

PHARMACOKINETIC AND EXPOSURE-RESPONSE ANALYSES BY REGION

To address the finding that the exposure-response analyses provided in the application did not allow determination of differences in drug and/or placebo effects between U.S. and non-U.S. subjects, GSK have conducted additional exposure-response analyses for the suggested endpoints.

Since region was not evaluated as a covariate in the original analyses either in terms of raw concentration-data review or correlation with individual parameter estimates, region was added to both the pharmacokinetic (PK) and PK-pharmacodynamic (PD) datasets for LAM100034. Seizure frequency data were separated by baseline and treatment phases and average cumulative seizure frequencies derived. In the revised analyses, region was added to the final PK model reported in HM2006/00631/00 and applied to LAM100034 data alone to assess potential PK and PK/PD differences between U.S. and non-U.S. subjects in this particular study. Clearance distributions were simulated using the revised final model. The individual predicted LTG concentration at the end of the maintenance period was derived as a measure of LTG exposure for the PK-PD analyses.

The exposure-response model was developed for continuous variables (seizure frequency and % change from baseline and for categorical variables (responders/non-responders). Three analyses were performed using different data forms of 1) seizure frequency data, baseline and on-treatment frequency counts, 2) percentage change from baseline and 3) probability of a $\geq$ 25 % and $\geq$ 50% change from baseline. A total of 202 subjects were included in the exposure-response data set.

Summary of Pharmacokinetic and Exposure-Response Analyses

Pharmacokinetic

- Serum LTG concentration ranges observed within each AED therapy group during the maintenance phase were generally similar in U.S. and non-U.S. subjects.

- Serum LTG concentrations in subjects receiving enzyme inhibitors were generally higher than those observed in other AED therapy groups (mixed, neutral or induced)

- Comparable dose ranges during the maintenance period were achieved in U.S. and non-U.S. subjects.

- Region as a covariate on oral clearance was not considered statistically or clinically significant.

- difference in the efficacy of LTG-XR in U.S. and non-U.S. subjects is unlikely to be as a consequence of differences in pharmacokinetics and resulting serum concentrations observed in the two groups.

Exposure-Response

- The concentration-response analysis of seizure frequency (baseline and on treatment) did not determine a regional difference.

- The concentration-response analysis of partial seizure frequency data using the percent decrease from baseline did not determine regional differences on either placebo or concentration-effect.

- The concentration-response analysis via logistic regression showed a clear relationship between the probability of a response with concentration; however, this was independent of region.

Reviewer Comments :

- I agree that generally that there was no clear difference in serum lamotrigine levels within each concomitant AED group based upon the US vs non-US patients. However, there were very few US patients in the VPA concomitant AED groups (VPA alone or VPA with a neutral AED, N=3 and VPA with an EIAED, N=1) to permit a reasonable comparison with those respective groups in the non-US patients (VPA alone or VPA with a neutral AED, N=16 and VPA with an EIAED, N=4) .

- I note that most of all of the PK comparisons for US vs non-US patients were based upon PK data derived from modeling rather than from actual observed PK data.

- The sponsor has not presented any compelling, convincing plots (for U.S. or non-U.S. patients) that clearly demonstrate a concentration-response suggesting a “dose” response and that increasing concentrations result in increasing efficacy responses. Such plots do not contain placebo data. If higher concentrations are not associated with increased efficacy responses, then the dosing employed may be producing concentrations that higher than those needed to achieve a maximal response. If this is true, correspondingly, patients may be taking larger doses of XR lamotrigine than are needed for optimal efficacy and may be at risk for increased toxicity/adverse reactions.

SPONSOR'S EXPLORATORY ANALYSES OF LAM100034 BY REGION

To address the Agency's concerns regarding apparent regional differences in study conduct, GSK re-monitored all U.S. and non-U.S. sites for 100% source document verification of the inclusion/exclusion criteria, primary endpoints (daily seizure counts), study drug dosing, adverse events, serious adverse events, vital signs, and concomitant medications. Although this monitoring did not result in significant changes in primary efficacy data, all changes have been incorporated into an amended CSR.

As reported in the amended CSR (RM2006/00035/01), an analysis of variance (ANOVA) was performed comparing the ranked percentage change from baseline in seizure frequency between treatment groups, controlling for country (analysis performed previously for the original NDA). The treatment effect was significant (p=0.008) (see Table 7.21, CSR), but there was no effect by individual country (p=0.849), and the treatment-by-country interaction (p=0.340) was not significant. This lack of individual country interaction does not explain the observed difference between U.S. and grouped non-U.S. sites. When this analysis is performed with grouped non-U.S. sites, the interaction with treatment is significant (p=0.0249).

In order to better understand the differences in treatment effect observed between U.S. and the grouped non-U.S. sites, GSK conducted several additional analyses of the primary efficacy endpoint using the amended data. Results of these analyses are provided below.

Comparison of Efficacy by Region and Study Phase

An analysis of the amended data set for LAM100034 was performed comparing U.S. and non-U.S. sites. The change from baseline in weekly seizure frequency for all partial seizures in escalation and maintenance phases are presented in Table 1 and Figure 1. The overall difference in median percent change in seizure frequency between U.S. and non-U.S. sites across the entire treatment period appears to be due, in part, to the differences observed in the escalation phase. In the escalation phase, the median percent reduction in seizure frequency for LTG-XR vs placebo in U.S. (18.9% vs 22.5%, p=0.7238) and non-U.S. sites (40.7% vs 14.3%, p=0.0113) was different, reaching statistical significance only in the non-U.S. sites. In contrast, during the maintenance phase, the median percent reduction in seizure frequency for LTG-XR vs placebo in U.S. (58.3% vs 33.3%, p=0.0376) and non-U.S. sites (63.0% vs 26.0%, p<0.0001) was similar and statistically significant in both regions.

Table 1 LTG-XR median percent change from baseline in seizure frequency by region and study phase

	U.S.			Non-U.S.		
Seizure Reduction (%)	Placebo	LTG-XR	p-value*	Placebo	LTG-XR	p-value*
Escalation	N=42	N=42		N=78	N=74	
Median	22.5	18.9	0.7238	14.3	40.7	0.0113
Maintenance	N=42	N=37		N=74	N=71	
Median	33.3	58.3	0.0376	26.0	63.0	<0.0001
Entire Treatment	N=42	N=42		N=78	N=74	
Median	28.9	36.3	0.5670	21.5	51.2	<0.0001

*P-value from an analysis of treatment effect for ranked percent change from baseline in weekly seizure frequency adjusting for ranked baseline.

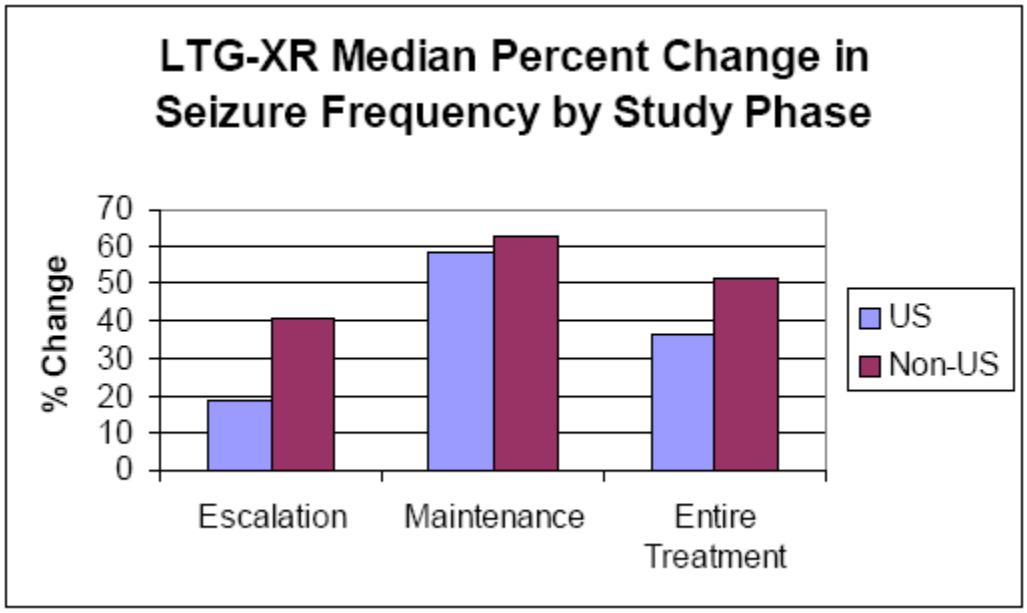
Reviewer Comment :

- These analyses show that the approximate arithmetic treatment difference/effect (XR lamotrigine – Placebo) of the median in the above Table is always greater for non – U.S. patients than for U.S. patients (for all groups of concomitant AEDs). The approximate treatment difference for the non-U.S. patients was 26 % for the dose escalation period, 47 % for the maintenance period, and 30 % for the entire study period. The approximate treatment difference for the U.S. patients was - 4 % for the dose escalation period, 25% for the maintenance period, and 7 % for the entire treatment period phase but was statistically superior to placebo only in the maintenance period for U.S. patients.

- Despite the fact that these are exploratory subgroup analyses it is desirable and good to see that the U.S. patients appeared to experience significant numerical efficacy but also nominally statistically significant benefit (without any multiplicity correction) in the maintenance period. Of interest, the efficacy of XR lamotrigine in each regional subgroup is relatively similar (i.e., 58 % for U.S., vs 63 % for non-U.S.) in the maintenance period.

- The most striking difference and disparity/discrepancy occurs in the dose escalation period and this difference also accounts for the difference in the entire period because that analysis combines respective results for the dose escalation and maintenance periods. Perhaps this discrepancy is related to the observation that the greater proportion of patients receiving VPA occurred in the non-U.S. patients and thereby they achieved a lower target XR lamotrigine and maximal lamotrigine dosing and PK steady state concentrations earlier than U.S. patients.

Figure 1 **LTG-XR median percent change from baseline in seizure frequency by region and study phase**



Reviewer Comment :

- In looking at the efficacy of XR lamotrigine based upon % seizure reduction without regard to respective placebo group, the effect was considerable for U.S. patients in the titration/escalation period, but much less than that for non-U.S. patients. In the maintenance period, the responses were similar for both subgroups. Because of the influence of the escalation period, the effect on the entire treatment period was less for U.S. patients. The difference may be related to the reasons outlined earlier by the sponsor.

Difference in the Use of Concomitant VPA

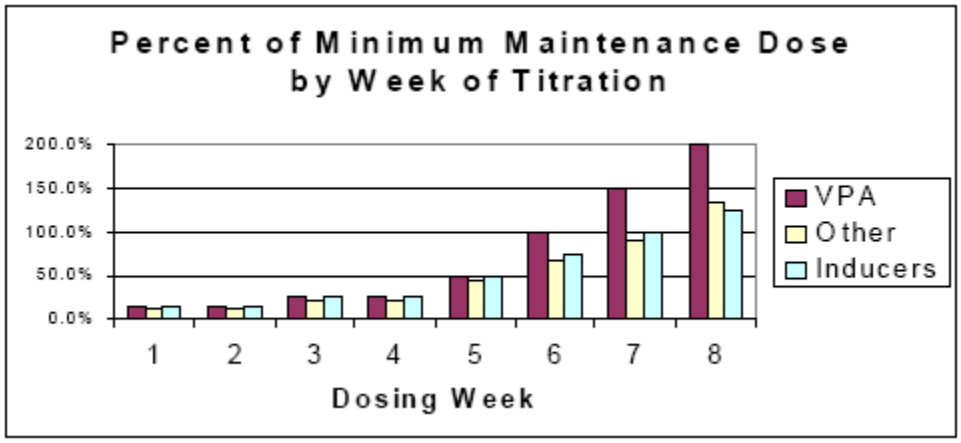
One difference between the U.S. and non-U.S. populations that was proposed as a potential explanation for the difference in efficacy observed during escalation was the relative difference in previous reports of better efficacy with VPA in combination with LTG than with other AEDs and the knowledge that the use of VPA for partial seizures was more common in non-U.S. sites than in the U.S sites. It was also hypothesized that the long titration period of seven weeks required to initiate treatment with LTG could result in the earlier onset of efficacy in the presence of concomitant VPA compared to other concomitant AEDs. The seven week titration period constituted 37% of the entire 19 week treatment period of this study.

The three dosing schedules for LTG take into account the differences in clearance of LTG between subjects taking concomitant VPA and those taking non-VPA regimens. Each of the dosing groups has a range of maintenance doses that have been associated with efficacy in clinical trials and in product labeling (100 to 200 mg per day for concomitant VPA, 400 to 500 mg per day for

concomitant enzyme-inducing AEDs, and 225 to 375 mg per day for other concomitant AEDs). The dosing regimen in this study adhered to current recommendations in the U.S. (Lamictal package insert) and non-U.S. regions (Lamictal summary of product characteristics) providing a seven week escalation for all subjects with target ranges that were in the middle or high end of the effective maintenance range for each AED group. The recommended dose escalation had the effect that subjects taking concomitant VPA reached the minimum maintenance dose of LTG 100 mg per day at the start of week 6 of the escalation, while subjects taking concomitant non-VPA regimens reached the minimum maintenance dose for LTG of 225 to 400 mg per day 1-2 weeks later. Subjects taking non-VPA regimens did not reach an initially effective treatment dose until the maintenance phase. Thus, beyond any putative synergistic or pharmacokinetic effects of concomitant VPA on LTG, the recommended dosing for LTG could result in an earlier response in subjects taking concomitant VPA (Figure 2).

This difference in VPA use between the U.S. and International (non-U.S.) regions is reflected in the International League Against Epilepsy (ILAE) treatment guidelines for initial treatment of partial seizures. The ILAE recommends carbamazepine, phenytoin or VPA as equal first line choices for the treatment of partial seizures [Glauser, 2006], while the expert consensus opinion in the U.S. does not rank VPA among the top 6 choices [Karceski, 2005].

Figure 2 Minimum maintenance dose by AED group during LAM100034



from LAM100034 in which only 4/42 (10%) U.S. subjects were taking concomitant VPA while 26/74 (35%) non-U.S. subjects were doing so (Figure 2). If indeed VPA subjects respond earlier than non VPA subjects, then this could explain why there was a better response in non-U.S. sites during escalation and subsequently, the entire treatment period.

Table 2 Use of VPA in U.S. and non-U.S. sites

	Utilization of VPA		
	U.S.	Non-U.S.	All
N	42	74	116
Any VPA	4 (10%)	26 (35%)	30 (26%)
Other AEDs	38 (90%)	48 (65%)	86 (74%)

Reviewer Comment :

- As outlined by the sponsor, there is no argument that there was a discrepancy in the percentage of patients receiving concomitant VPA between both regions with a much greater proportion of non-U.S. patients receiving VPA.

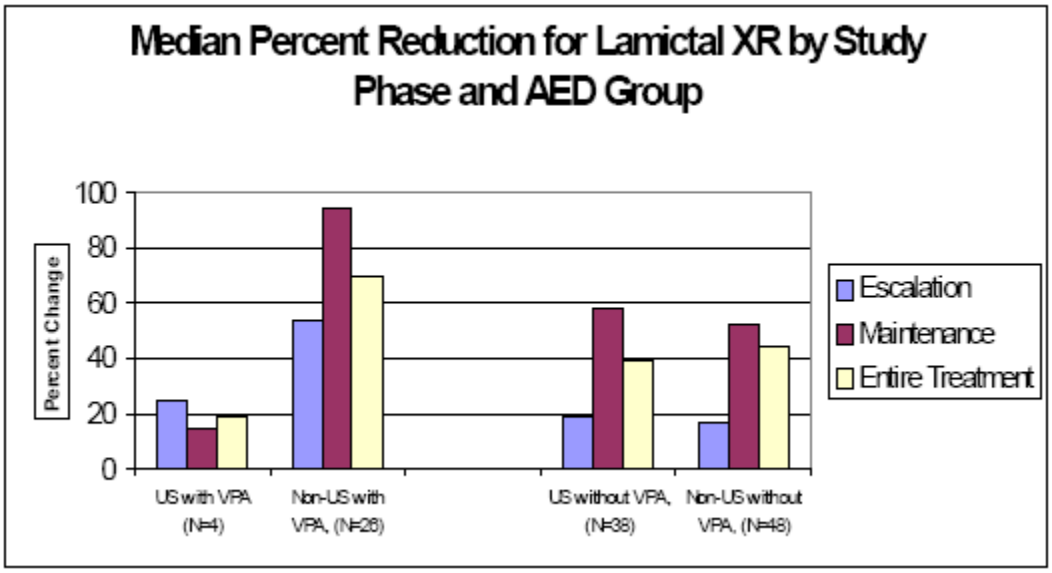
Difference in Efficacy Related to VPA Use

There are two ways in which concomitant VPA may contribute to a difference in efficacy with LTG in comparison with other AEDs. (1) VPA is an inhibitor of LTG clearance resulting in a reduction in clearance by one half on the average. While the doses of LTG used with concomitant VPA are reduced to account for this interaction, there is considerable inter-individual variability in the degree to which VPA inhibits LTG clearance. (2) As noted above, the recommended titration schedule for subjects taking concomitant VPA results in those subjects reaching minimally effective doses sooner than those taking other AEDs. Table 3 and Figure 3 illustrate the relative contribution of concomitant VPA to the response to LTG. Unfortunately, with 26/30 (87%) of the VPA subjects in the study coming from non-U.S. sites, the small number of remaining subjects from U.S. sites taking concomitant VPA (N=4) limits the meaningfulness of an analysis directly comparing U.S. and non-U.S. responses based on concomitant VPA. However, among subjects taking non-VPA regimens, there was virtually no difference in the median percent change in seizure frequency for LTG-XR between U.S. and non-U.S. sites in either study phase. The impact of the imbalance of concomitant VPA use is reflected in the difference between U.S. and non-U.S. response in the presence of concomitant VPA.

Table 3 LTG-XR median percent change in seizure frequency by region, study phase and VPA use

	VPA		non-VPA	
Seizure Reduction (%)	U.S. Sites	Non-U.S. Sites	U.S. Sites	Non-U.S. Sites
Escalation	N=4	N=26	N=38	N=48
Median	24.6	54.3	18.9	16.8
Maintenance	N=4	N=25	N=33	N=46
Median	14.5	93.9	58.3	52.3
Entire Treatment	N=4	N=26	N=38	N=48
Median	18.6	69.9	39.5	44.2

Figure 3 LTG-XR median percent change in seizure frequency by region, study phase and VPA use



The better response for subjects taking VPA is likely also attributable to the higher LTG concentrations compared to those subjects taking non-VPA regimens (Table 4).

Reviewer Comment :

- The results shown in the above figure 3 suggests that there was a major discrepancy in the efficacy for the small number of U.S. patients treated with concomitant VPA relative to the non-U.S. patients. However, results for patients without concomitant VPA were relatively similar for all 3 phase/period analyses.

Table 4 LTG concentration by region and concomitant AED

	U.S.			non-U.S.		
	N[1]	Median (ug/mL)	Mean (ug/mL)	N[1]	Median (ug/mL)	Mean (ug/mL)
Overall	126	4.11	4.71	283	5.05	6.34
VPA with inducer	4	3.86	3.84	19	3.52	4.11
VPA alone or with a non-inducer	12	7.04	8.10	73	9.37	8.32
Inducer AED alone or without VPA	75	3.96	4.36	140	4.79	5.40
All other regimens	35	4.10	4.39	51	4.71	6.91

1. N = number of samples obtained (on average three per subject were collected)

These findings indicate that the U.S. vs non-U.S. difference in efficacy during the escalation phase is in large part attributable to the greater number of subjects taking concomitant VPA in the non-U.S. population and the better response these subjects had compared to subjects not taking VPA. Thus, similar responses to LTG therapy would only be expected once the subject population had achieved

the target LTG doses. Indeed, in the maintenance phase of this study, response to therapy is similar between U.S. and non-U.S. sites.

Reviewer Comment :

- In general, serum lamotrigine concentrations of U.S. patients were lower for all subgroup compared to those for non-U.S. patients but these results, I believe, were somewhat confounded by combining results from the escalation and maintenance phases. Reasons for relatively lower levels for U.S. patients in the escalation period have been noted. These results also compare the total number of samples in each group not necessarily the mean nor median of each of the patients in each group. Of interest some subsequent analyses discussed later in this review, suggest that serum lamotrigine levels of the respective concomitant AED groups were generally similar for U.S. and non-U.S. patients in the maintenance period when PK steady state had been achieved.

Placebo Response

There was a higher placebo response in U.S. subjects. Evaluating only subjects using non-VPA regimens, some difference in median percent change from baseline in seizures over the entire treatment period between U.S. and non-U.S. sites remains . However, the median percent change from baseline in seizure frequency in the LTG treated subjects is similar for all treatment phases for both regions.

Table 5 Median percent change from baseline in seizure frequency by region and study phase for subjects not taking VPA

	U.S. Sites			non-U.S. Sites		
Seizure Reduction (%)	Placebo	LTG-XR	p-value*	Placebo	LTG-XR	p-value*
Escalation	N=32	N=38		N=45	N=48	
Median	22.5	18.9	0.7391	14.3	16.8	0.3514
Maintenance	N=32	N=33		N=43	N=46	
Median	39.3	58.3	0.0971	25.0	52.3	0.0004
Entire Treatment	N=32	N=38		N=45	N=48	
Median	34.1	39.5	0.6950	15.8	44.2	0.0100

* P-value from an analysis of treatment effect for ranked percent change from baseline in weekly seizure frequency adjusting for ranked baseline.

Reviewer Comment :

- There were a substantial number of patients in each subgroup who had taken concomitant AEDs excluding VPA. As noted by the sponsor, the main difference in these results were that the placebo "response" for these patients was much greater for U.S. patients vs non-U.S.

patients. However. The XT lamgotrigine responses were quite similar for both subgroups. These results further suggest that the increased placebo "response" observed in U.S. patients may have played a major role in accounting for the difference in the treatment difference of U.S. vs non-U.S. patients.

Evaluating only subjects using VPA regimens (Table 1), there are too few subjects in the U.S. sites to allow for a meaningful comparison. In the non-U.S. sites, improved responses are seen in all phases of the study, as expected in the subjects using VPA regimens, due to higher serum levels in these subjects.

Table 6 Median percent change from baseline in seizure frequency by region and study phase for subjects taking VPA

	U.S. Sites			non-U.S. Sites		
Seizure Reduction (%)	Placebo	LTG-XR	p-value*	Placebo	LTG-XR	p-value*
Escalation	N=10	N=4		N=33	N=26	
Median	13.7	24.6	0.9120	14.3	54.3	0.0016
Maintenance	N=10	N=4		N=31	N=25	
Median	20.0	14.5	0.4688	26.9	93.9	0.0002
Entire Treatment	N=10	N=4		N=33	N=26	
Median	18.1	18.6	0.6237	24.2	69.9	<0.0001

* P-value from an analysis of treatment effect for ranked percent change from baseline in weekly seizure frequency adjusting for ranked baseline.

Reviewer Comment :

- I agree that the small number of U.S. patients using concomitant VPA makes it difficult to make any meaningful comparison.

Additional Exploratory Analyses

The following other possible explanations for the differences between the U.S. and non-U.S. results were explored but did not lead to any conclusive findings:

- Differences in medical refractoriness to treatment
- Differences in use of old vs new AEDs
- Differences in baseline seizure frequency
- Differences in demography

- Differences in LTG average maintenance doses
- Differences in days on treatment and premature discontinuation rates
- Differences in partial seizure type

Upon reviewing these additional analyses, only differences in medical refractoriness between U.S. and non-U.S. regions held the potential to explain differences in efficacy and therefore were investigated further. As noted above, exploration into this dimension was inconclusive; however, some interesting and relevant information was discovered and has been provided below for potential consideration.

Refractoriness to AED Therapy

Medical intractability to AED therapy has been defined as the failure of 2 AEDs in patients with partial epilepsy who are epilepsy surgery candidates [Wiebe, 2001]. This definition is based on clinical experience and has previously not been prospectively studied. A recent publication by Schiller [Schiller, 2008] has prospectively quantified the response to AED therapy as a function of the number of failed AEDs in epilepsy. Prognostic factors to newly administered AED therapy were developed based on prior AED treatment history. In this study, 97% of the patients were 16 years of age or older, and 74% of the patients had a diagnosis of partial epilepsy, 18% had idiopathic generalized epilepsy and 8% had either symptomatic generalized epilepsy or undetermined epilepsy type. Seizure freedom over the last 12 months of follow up in newly diagnosed patients with epilepsy was 62%, which progressively decreased to 42%, 17% and 0%, after use of 1, 2 to 5, or 6 to 7 previous AEDs, respectively. Additionally, 50% seizure reduction over the last 3 months of follow up in newly diagnosed patients with epilepsy was 86%, which also progressively decreased to 69%, 47%, and 31%, after use of 1, 2 to 5, or 6 to 7 previous AEDs, respectively. The authors concluded their study by defining 'relative AED drug resistance' in epilepsy as having failed 2 past AEDs, and by defining 'absolute AED drug resistance' as the failure of 6 or more AEDs. Additional factors which resulted in worse outcomes included duration of the subject's epilepsy and the number of seizures that the subjects had in the 3 months prior to initiation of the newly administered AED treatment.

In parallel with the Schiller study, the relative refractoriness of each patient in LAM10034 was estimated by combining the number of AEDs each subject reported to have taken prior to enrollment, with the number of AEDs each subject was taking concomitantly at enrollment, summing only unique exposures. These numbers varied from a minimum of one to more than six. It was not possible to determine which AEDs had failed due to lack of efficacy and which had failed for tolerability problems, a distinction that was made in the Schiller study. Determination of the number of failed AEDs is largely based on patient recall but nevertheless provides broad measure of refractoriness that is similar to that used by Schiller.

In comparing the results of LAM100034 to the Schiller study, the >=50% seizure reduction rate from baseline was compared between U.S. and non-U.S. sites. However, as can be seen in Table 7, there are too few subjects in the groups that had failed 1 or >=6 AEDs, and meaningful comparisons of this data set with the Schiller article are difficult to interpret.

Table 7 Comparison of number of failed AED concomitant medications by U.S. or non-U.S. sites (maintenance period)

	U.S. Sites	Non-U.S. Sites
Number of Failed AEDs	LTG XR N=37	LTG XR N=71
1	4 (11%)	12 (17%)
2 to 5	21 (57%)	55 (77%)
6 or more	12 (32%)	4 (6%)

Schiller also evaluated the impact on response of seizure frequency in the 3 months prior to AED initiation (Figure 4). The subjects in LAM100034 from U.S. sites had failed on average 4 AEDs compared to subjects from non-U.S. sites who had failed 3 prior AEDs. Unfortunately, enrollment criteria for LAM100034 required that subjects have at least 12 partial seizures in the 3 months prior to start of study drug. This number of prior baseline seizure frequency places LAM100034 data on the flat insensitive portion of the evaluation curve. What is clear, however, is that there is an imbalance between U.S. and non-U.S. sites in the percent of subjects who would be classified by Schiller as having 'absolute AED drug resistance' (32% for U.S. sites, 6% for non-U.S. sites).. While the comparison of the LAM100034 data to the Schiller article presents some difficulties, the information may still provide some insight into a potential contribution to the differences seen across regions.

Reviewer Comment :

- The data shown in Table 7 suggest that U.S. patients had a smaller percentage of patients (57 %) who had "failed" treatment on 2-5 previous AEDs compared to non-U.S. patients (77 %). Table 7 also suggest that a higher percentage of U.S. patients (32%) had "failed" on 6 previous AEDs compared to non-U.S. patients (6 %).

- However, it is not clearly known if the number of "failed" AEDs was related to problems with efficacy or safety/tolerability and if inadequate efficacy was truly established because the patient did not have a good therapeutic response after being on an appropriate dose for a reasonably appropriate period. Thus, it is difficult to make too much of these data analyses.

Figure 4 Effect of seizure frequency in the 3 months prior to AED initiation on the response to new AED therapy [Schiller, 2007]

Sponsor Conclusions

- Any difference in the efficacy of LTG-XR in U.S. and non-U.S. subjects is unlikely to be as a consequence of differences in pharmacokinetics and resulting serum concentrations observed in the two groups.

- There was an imbalance in the use of concomitant VPA between U.S. and non-U.S. sites with 87% of the VPA use occurring at non-U.S. sites, which is consistent with known regional differences in treatment of partial seizures.

- Concomitant VPA use together with a seven-week escalation phase appears to facilitate an earlier response to treatment with LTG-XR in combination with VPA which also contributes to a better response over the entire treatment period.

- In spite of the disproportionate contribution of VPA to the non-U.S. response, the response to treatment was statistically significant in both regions during the maintenance phase.

- These effects of VPA are similar to those observed in previously conducted trials with LTG.

- For non VPA subjects, the median seizure reduction in the maintenance phase is similar, reaching statistical significance for the non-U.S. sites with a trend in the U.S. sites, possibly related to a higher placebo response in the U.S.

Reviewer Comment :

- The disproportionately increased percentage of patients who were randomized to XR lamotrigine and VPA (with or without other AEDs)and who achieved highest serum lamotrigine levels in non-U.S. patients (compared to U.S. patients) may have contributed at least partially to the much larger treatment effect/difference (XR lamotrigine result – placebo result) of XR lamotrigine for foreign vs U.S patients.

- To try to provide more insight into possible efficacy of U.S. patients, I asked the sponsor to conduct and submit multiple, additional efficacy analyses (for cumulative efficacy throughout the whole study period and for efficacy in defined epochs throughout the escalation, maintenance periods) in various subgroups according to concomitant AED treatment. We also asked the statistical reviewer, Dr. Tristan Massie, to verify these analyses. The efficacy analyses were also conducted for all observed data and for observed data in completers. Overall, the completer analyses were generally quite similar to results for all observed data. In view of this observation, I have presented only the completer analyses that were performed by Dr. Massie, our statistical reviewer. The following tables show the median treatment difference for these various subgroup analyses for cumulative efficacy and for efficacy over various epochs throughout the whole study period.

Table 1 **Cumulative Analyses : Treatment Difference/Effect (XL Lamotrigine % - Placebo %) for Percent Reduction in Weekly Seizure Frequency From Baseline Up To Indicated Week for Completers According to Concomitant AED Group**

	ANY CONCOMITANT AED		VPA WITH EIAEDS		VPA ALONE		EIAEDS ALONE		ALL OTHER ("NEUTRAL" AEDS)	
	US	Non-US	US	Non-US	US	Non-US	US	Non-US	US	Non-US
Time/ Epoch	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P
Base Line WSR	2.7 P/2.6XL (P39/XL34)	2 P/2.3XL (P69/XL63)	2 P/1.8XL (P4/XL1)	2.3 P/2XL (P18/XL4)	2.7 P/16XL (P5/XL3)	2.3 P/2.1XL (P11/XL16)	3 P/2.3XL (P14/XL19)	1.5 P/2.5XL (P23/XL31)	3.5 P/3.2XL (P16/XL11)	2.1 P/1.7XL (P17/XL12)
Wk 3	10/15 (P39/XL34) |0.266	16/20 (P69/XL63) |0.035	3/3 (P4/XL1) |1	28/23 (P18/XL4) |0.25	-20/-26 (P5/XL3) |0.371	40/42 (P11/XL16) |0.109	5/26 (P14/XL19) |0.236	10/7 (P23/XL31) |0.54	20/12 (P16/XL11) |0.675	18/21 (P17/XL12) |0.506
7	14/13 (P39/XL34) |0.147	26/21 (P69/XL63) |0.005	66/66 (P4/XL1) |0.289	35/32 (P18/XL4) |0.115	-34/-34 (P5/XL3) |0.371	45/43 (P11/XL16) |0.036	13/18 (P14/XL19) |0.105	11/9 (P23/XL31) |0.306	12/4 (P16/XL11) |0.711	2/20 (P17/XL12) |0.492
11	10/7 (P39/XL34) |0.479	29/26 (P69/XL63) |0	35/35 (P4/XL1) |0.289	40/40 (P18/XL4) |0.009	-50/-50 (P5/XL3) |0.371	39/43 (P11/XL16) |0.032	0/10 (P14/XL19) |0.455	15/20 (P23/XL31) |0.077	3/-1 (P16/XL11) |0.902	32/25 (P17/XL12) |0.223
15	9/8 (P39/XL34) |0.413	38/28 (P69/XL63) |0	16/16 (P4/XL1) |0.289	41/37 (P18/XL4) |0.019	-23/-23 (P5/XL3) |0.551	43/46 (P11/XL16) |0.019	5/10 (P14/XL19) |0.5	30/23 (P23/XL31) |0.057	13/1 (P16/XL11) |0.941	40/24 (P17/XL12) |0.127
19	12/9 (P39/XL34) |0.344	35/31 (P69/XL63) |0	-26/-26 (P4/XL1) |0.289	43/40 (P18/XL4) |0.019	-13/-13 (P5/XL3) |0.766	66/52 (P11/XL16) |0.01	3/10 (P14/XL19) |0.434	31/21 (P23/XL31) |0.061	8/4 (P16/XL11) |0.786	44/34 (P17/XL12) |0.08

WSR – Weekly seizure rate
Diff = Arithmetic difference of medians (XL LTG % - Placebo %)
HL= Hodge-Lehman estimate of difference of medians (XL LTG % - Placebo %)
p-value of 0 means <0.001

Table 2 (Continued) Cumulative Analyses : Treatment Difference/Effect (XL Lamotrigine % - Placebo %) for Percent Reduction in Weekly Seizure Frequency From Baseline Up To Indicated Week for Completers According to Concomitant AED Group

	EXCLUDING VPA ALONE		EXCLUDING ALL VPA	
	US	Non-US	US	Non-US
Time/ Epoch	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P
Base Line WSR	3 P/2.3XL (P34/XL31)	2 P/2.3XL (P58/XL47)	3.4 P/2.4XL (P30/XL30)	1.9 P/2.4XL (P40/XL43)
Wk 3	16/23 (P34/XL31) |0.126	9/12 (P58/XL47) |0.193	15/21 (P30/XL30) |0.191	13/13 (P40/XL43) |0.253
7	26/18 (P34/XL31) |0.054	10/15 (P58/XL47) |0.05	15/14 (P30/XL30) |0.139	10/13 (P40/XL43) |0.124
11	13/11 (P34/XL31) |0.253	29/23 (P58/XL47) |0.003	8/6 (P30/XL30) |0.525	24/22 (P40/XL43) |0.017
15	13/12 (P34/XL31) |0.27	33/23 (P58/XL47) |0.002	7/8 (P30/XL30) |0.46	35/23 (P40/XL43) |0.009
19	15/11 (P34/XL31) |0.232	33/26 (P58/XL47) |0.001	9/10 (P30/XL30) |0.322	34/25 (P40/XL43) |0.005

WSR – Weekly seizure rate
Diff = Arithmetic difference of medians (XL LTG % - Placebo %)
HL= Hodge-Lehman estimate of difference of medians (XL LTG % - Placebo %)
p-value of 0 means <0.001

Table 2 **Non-Cumulative Analyses : Treatment Difference/Effect (XL Lamotrigine % - Placebo %) for Percent Reduction in Weekly Seizure Frequency From Baseline For Indicated Week Epochs for Completers According to Concomitant AED Group**

	ANY CONCOMITANT AED		VPA WITH EIAEDS		VPA ALONE		EIAEDS ALONE		ALL OTHER ("NEUTRAL" AEDS)	
	US	Non-US	US	Non-US	US	Non-US	US	Non-US	US	Non-US
Time/ Epoch	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P
Baseline Weekly Seizure Rate (WSR)	3 P/3XL (P39/XL34)	2 P/2XL (P69/XL63)	2 P/2XL (P4/XL1)	2 P/2XL (P18/XL4)	3P/16XL (P5/XL3)	2 P/2XL (P11/XL16)	3 P/2XL (P14/XL19)	2 P/3XL (P23/XL31)	4 P/3XL (P16/XL11)	2 P/2XL (P17/XL12)
Wks 1-3	10/15 (P39/XL34) |0.248	16/18 (P69/XL63) |0.041	0/0 (P4/XL1) |1	26/21 (P18/XL4) |0.25	-20/-27 (P5/XL3) |0.371	38/37 (P11/XL16) |0.12	6/26 (P14/XL19) |0.222	10/7 (P23/XL31) |0.523	21/13 (P16/XL11) |0.711	17/21 (P17/XL12) |0.478
4-7	15/14 (P39/XL34) |0.127	18/21 (P69/XL63) |0.016	88/88 (P4/XL1) |0.289	24/27 (P18/XL4) |0.115	-38/-36 (P5/XL3) |0.233	64/37 (P11/XL16) |0.077	21/22 (P14/XL19) |0.113	6/12 (P23/XL31) |0.377	8/5 (P16/XL11) |0.675	15/11 (P17/XL12) |0.506
8-11	11/0 (P39/XL34) |0.969	35/36 (P69/XL63) |0	-13/-13 (P4/XL1) |0.724	73/65 (P18/XL4) |0.014	-46/-45 (P5/XL3) |0.766	40/28 (P11/XL16) |0.059	13/-5 (P14/XL19) |0.675	42/25 (P23/XL31) |0.045	12/6 (P16/XL11) |0.863	35/39 (P17/XL12) |0.075
12-15	34/16 (P39/XL34) |0.098	34/29 (P69/XL63) |0	-46/-46 (P4/XL1) |0.289	47/40 (P18/XL4) |0.089	22/6 (P5/XL3) |1	55/38 (P11/XL16) |0.006	40/14 (P14/XL19) |0.172	39/25 (P23/XL31) |0.076	25/15 (P16/XL11) |0.473	34/32 (P17/XL12) |0.096
16-19	17/7 (P39/XL34) |0.461	56/41 (P69/XL63) |0	-241/-241 (P4/XL1) |0.289	68/60 (P18/XL4) |0.027	19/6 (P5/XL3) |0.766	92/79 (P11/XL16) |0.017	12/0 (P14/XL19) |0.956	26/23 (P23/XL31) |0.089	10/16 (P16/XL11) |0.443	68/68 (P17/XL12) |0.004

WSR – Weekly seizure rate
Diff = Arithmetic difference of medians (XL LTG % - Placebo %)
HL= Hodge-Lehman estimate of difference of medians (XL LTG % - Placebo %)
p-value of 0 means <0.001

Table 2 (Continued) Non-Cumulative Analyses : Treatment Difference/Effect (XL Lamotrigine % - Placebo %) for Percent Reduction in Weekly Seizure Frequency From Baseline For Indicated Week Epcohs for Completers According to Concomitant AED Group

	EXCLUDING VPA ALONE		EXCLUDING ALL VPA	
	US	Non-US	US	Non-US
Time/ Epoch	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P	Diff/HL N1/N2 P
Base Line WSR	3 P/2XL (P34/XL31)	2 P/2XL (P58/XL47)	3 P/2XL (P30/XL30)	2 P/2XL (P40/XL43)
Wks 1-3	20/22 (P34/XL31) |0.116	9/12 (P58/XL47) |0.191	17/21 (P30/XL30) |0.171	13/12 (P40/XL43) |0.236
4-7	16/18 (P34/XL31) |0.051	12/13 (P58/XL47) |0.127	15/15 (P30/XL30) |0.119	9/13 (P40/XL43) |0.218
8-11	12/3 (P34/XL31) |0.818	34/34 (P58/XL47) |0	17/0 (P30/XL30) |0.97	28/29 (P40/XL43) |0.008
12-15	37/16 (P34/XL31) |0.11	26/24 (P58/XL47) |0.009	38/16 (P30/XL30) |0.108	30/25 (P40/XL43) |0.012
16-19	16/7 (P34/XL31) |0.457	44/36 (P58/XL47) |0	15/9 (P30/XL30) |0.402	39/34 (P40/XL43) |0.002

WSR – Weekly seizure rate
Diff = Arithmetic difference of medians (XL LTG % - Placebo %)
HL= Hodge-Lehman estimate of difference of medians (XL LTG % - Placebo %)
p-value of 0 means <0.001

Reviewer Comment :

- These analyses show that non-US responses to XR lamotrigine were generally greater than those for U.S patients for various subgroups.

- In some instances the arithmetic treatment difference (XR lamotrigine – Placebo) of medians was similar to the magnitude of the Hodge Lehman estimate of median of the difference but in others it was quite discrepant.

- The treatment difference for various concomitant AED groupings for U.S patients often shows some considerable numerical effects of XR lamotrigine suggesting efficacy.

- The baseline seizure rates were generally quite similar for all subgroups with one exception, the XR lamtorigine group for U.S. patients taking concomitant VPA "alone" was much higher (~ 16) than that for the respective placebo patients (~ 3). Thus, this comparison is not a very good or appropriate one.

- **The VPA subgroups (i.e. VPA "alone" or VPA with EIAEDs) for U.S. patients are problematic in various comparisons for a few reasons.** First, the number of U.S. patients in the VPA subgroups was relatively small. There were only 3 patients receiving XR lamotrigine and 5 patients placebo in the VPA alone subgroup. The VPA with EIAEDs subgroup was even small with only one patient receiving XR lamotrigine and 4 patients receiving placebo. The non-U.S. group for VPA "alone" was much larger with 27 patients (XR lamotrigine 16, placebo 11) as was the VPA with EIAEDs subgroup that included 22 patients (XR lamotrigine 4, placebo 18). Second, the baseline seizure rates were extremely different as noted above for U.S. patients in the VPA "alone." Some of these VPA subgroups for U.S. patients did not show reductions in seizures but rather increases in seizure rates.

- Because of the large difference in baseline seizures for U.S. patients treated with VPA "alone," this subgroup was excluded from some analyses. When the U.S. subgroup for VPA "alone" was excluded from analyses the results were not greatly different than those showing results for U.S. patients in which any VPA was used.

- The treatment difference/effect for efficacy results over epochs, particularly in the maintenance period, was often more substantial than analyses shown by the cumulative assessment of efficacy.

- The efficacy suggested in the last epoch (weeks 15-19) of the maintenance period for U.S, patients was often lower than the efficacy suggested in the previous epoch (weeks 11-15).

- The analyses in which patients taking any VPA were excluded (e.g., patient on EIAEDs and "neutral" AEDs) suggested some efficacy of XR lamotrigine.

- For U.S. patients excluding any VPA use in the cumulative analysis at the end of the study (week 19), the arithmetic treatment effect/difference of the medians was 9 % and the Hodge Lehman estimate of the median of difference was 10 %.

- For U.S. patients excluding any VPA use in the non-cumulative analysis of epoch at the end of the study (weeks 15 - 19), the arithmetic treatment effect/difference of the medians was 15 % and the Hodge Lehman estimate of the median of the difference was 9 %.

- These analyses suggested greater numerical efficacy than had been suggested initially (e.g., ~ 4 %) for the estimate of the median of the difference for all U.S. patients.

The following tables show the cumulative efficacy and the non-cumulative efficacy over epochs in the maintenance period for all observed data and for observed data in completers according to the placebo result and the XR lamotrigine result for all U.S. and all non-U.S. patients who were treated with concomitant AED(s) excluding VPA.

Table Median Placebo / XR Lamotrigine Cumulative % Reduction from Baseline in Weekly Seizure Rate (WSR) by Non-VPA Concomitant AED and Visit in Maintenance Phase for ALL Patient Observed Data and for ALL Completers (P #/ XL # indicates N per each group)

			EIAEDs alone or with-out LTG altering AEDs		All Other regimens		
All Observed Data			US Pts	Non-USPts		US Pts	Non-USPts
Median Baseline/Pre-Treatment WSR			(P16/ XL24)	(P27/ XL35)		(P16/ XL14)	(P18/ XL13)
Median Change from Baseline							
Visit 6 (11 Wks)			23/25 (P16/ XL21)	18/35 (P25/ XL33)		19/32 (P16/ XL12)	8/21 (P18/ XL13)
Visit 7 (15 Wks)			28/39 (P15/ XL19)	17/36 (P23/ XL33)		31/36 (P16/ XL12)	10/38 (P17/ XL12)
Visit 8 (19 Wks)			31/45 (P13/ XL19)	20/42 (P23/ XL31)		35/35 (P16/ XL11)	13/51 (P17/ XL12)
Completer Data							
Median Baseline/Pre-Treatment WSR			(P13/ XL19)	(P23/ XL31)		(P16/ XL11)	(P17/ XL12)
Median Change from Baseline							
Visit 6 (11 Wks)			39/60	19/56		40/44	31/74
Visit 7 (15 Wks)			31/80	20/56		35/47	33/70
Visit 8 (19 Wks)			55/63	38/53		22/33	25/90

Median % Reduction from Baseline for each treatment was rounded off

Table Median Placebo / XR Lamotrigine % Reduction from Baseline in Weekly Seizure Rate (WSR) Over Various Time Epochs in Maintenance Phase by Non-VPA Concomitant AED and Visit for ALL Patient Observed Data and for ALL Completers (P #/ XL # indicates N per each group)

			EIAEDs alone or with-out LTG altering AEDs		All Other regimens	
All Observed Data		US Pts	Non-USPts		US Pts	Non-USPts
Median Baseline/Pre-Treatment WSR		(P16/ XL24)	(P27/ XL35)		(P16/ XL14)	(P18/ XL13)
Median Change from Baseline						
Weeks 8-11		17/32 (P16/ XL21)	18/36 (P25/ XL33)		19/32 (P16/ XL12)	9/32 (P18/ XL13)
Weeks 12-15		30/42 (P15/ XL19)	17/39 (P23/ XL33)		31/37 (P16/ XL12)	13/46 (P17/ XL12)
Weeks 16-19		35/47 (P15/ XL19)	20/46 (P23/ XL31)		35/35 (P16/ XL11)	16/57 (P17/ XL12)
Completer Data						
Median Baseline/Pre-Treatment WSR		N (P13/ XL19)	N (P23/ XL31)		N (P16/ XL11)	N (P17/ XL12)
Median Change from Baseline						
Weeks 8-11		41/56	19/56		40/42	42/62
Weeks 12-15		30/80	20/56		35/47	33/70
Weeks 16-19		55/63	38/53		22/33	25/90

Median % Reduction from Baseline for each treatment was rounded off

Reviewer Comment :

- These results for the XR lamotrigine for both the cumulative and non-cumulative analyses often show that the U.S. result is substantial in absolute % seizure reduction and in some instances even greater than that for non-U.S patients. However, the placebo results for U.S. patients is commonly greater than that for non-U.S. patients. These results

derived from patients who were not treated with any VPA removes the potential confounding effect of VPA and the disproportionate percentage of VPA patients between U.S. and non-U.S. patients. These analyses in particular support the possibility or speculation that the main reason for the small numerical treatment effect/difference for U.S. patients may be primarily related to the "excessive" placebo "response" in U.S. patients.

Summary Conclusion of Statistical Reviewer (Dr. Tristan Massie) from Additional Efficacy Analyses of Mainly Subgroups (US vs non-US, and various concomitant AED subgroups) derived from 4/10/09 Memo

In all of the concomitant AED subgroups considered the treatment effect was larger in the pool of non-U.S. sites than in the pool of U.S. sites. While the median percent reduction in seizure frequency for placebo was typically higher in the U.S. in these subgroups, i.e., there was a higher placebo effect, the median percent reduction for Lamictal was also lower in the U.S. than non-U.S. in several cases. It is not clear to this reviewer from the clinical data that the regional difference in treatment effects is due to the regional difference in VPA use. In conclusion, the lower efficacy in the U.S. was fairly consistent across the concomitant AED subgroups and while it may be possible to generate hypotheses for the underlying cause of the observed regional difference it is not possible to conclusively establish a causal relationship on the basis of the existing data. It is also important to keep in mind that there are many well known limitations of subgroup analyses that must be considered when evaluating subgroup analyses.

Sponsor's Exposure-Response Analyses

FDA Comment:
"It is possible, however, that additional exposure-response analyses comparing data from all U.S. sites vs all foreign sites might be helpful.

In this regard, we note that the general approach that you have taken to describe the exposure-response for XR lamotrigine is reasonable, but the analyses that you have submitted do not allow us to decide whether there are differences in drug effects (and placebo effects) between U.S. and non-U.S./foreign sites.

We recommend that you extend your Cmin-response analyses to investigate any potential U.S. and non-U.S. differences both in placebo and drug effects. It might be helpful to substantiate your findings with several sensitivity analyses using Study 34 study data for this purpose. Specifically, please conduct the exposure-response analyses for the following endpoints, in addition to any that you consider relevant. Please submit a detailed report showing relevant diagnostic plots, parameter estimates and their precision including mean, variance and SEs for all parameters and confidence intervals for slopes.

1) Seizure frequency rate % change from baseline during the double-blind phase (escalation and maintenance phases).

2) Response rate (> or = 25%, > or = 50%).

3) *Test whether there are PK differences between U.S. and non-U.S. sites.* "

GSK Summary Response:
To address the comment that the exposure-response analyses provided in the application did not allow determination of differences in drug and/or placebo effects between U.S. and non-U.S. subjects in study **LAM10034**, GSK has conducted additional exposure-response analyses for the suggested endpoints; details are provide in Report HM2007/00638/00. These analyses revealed no differences in exposure-response between U.S. and non-U.S. subjects to explain the apparent regional differences in efficacy.

Selected Information from the Sponsor's Report HM2007/00638/00 Relating to Exposure-Response Analyses :

Visual Evaluation of Serum Concentration-Time Data

Serum lamotrigine concentration data versus time after dose was summarized and plotted for study LAM100034, by region (defined as U.S. and non-U.S.), and by anti-epileptic co-medication (Induced, Inhibited, Neutral and Mixed), as summarized in Table 4-1.

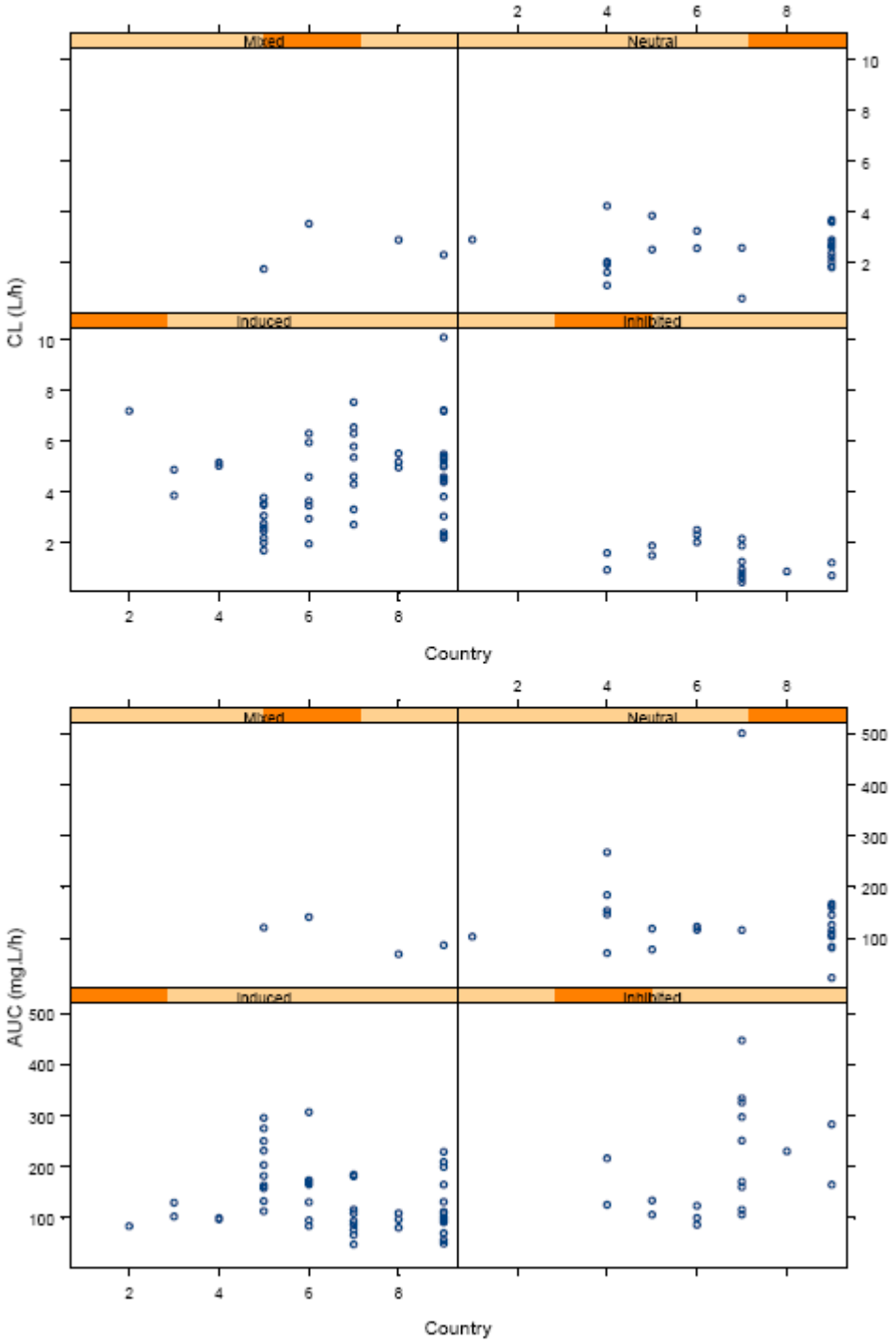
Table 4-1: Summary table of Categorization of Anti-Epileptic Drug Therapy

Definition	*Concomitant AED Therapy*
Induced	Carbamazepine, phenytoin, phenobarbital or primidone
Inhibitor	Valproic acid
Neutral	No administration of AEDs that induced or inhibited
Mixed	Carbamazepine, phenytoin, phenobarbital or primidone in combination with valproic acid

Effect of Region on Clearance
(from sponsor response 7/10/08 for exposure-response doc)

Posthoc estimates of individual predicted oral clearance and area-under the curve (AUC) from the base model without Subject 22, by country, are presented in Figure 11-19 for subjects on enzyme inhibitors, inducers, neutral and mixed AEDs, respectively. Boxplots by region (U.S. versus non-U.S.) are presented in Figure 11-20, for subjects on enzyme inducers, inhibitors neutral and mixed AEDs, respectively.

Figure 11-19: Summary Plot of Posthoc Estimates of Lamotrigine Oral Clearance (CL/F(L/h)) and AUC (mg.h/L) versus Country ID (1-9) by AED co-medication (Induced, Inhibited, Neutral and Mixed)



1=Argentina, 2=Brazil, 3=Chile, 4=Germany, 5=India, 6=Korea, 7=Russian Federation, 8=Ukraine, 9=United States

Reviewer Comment :

- Figure 11-19 suggests that there is no clear difference of lamotrigine clearance or AUC exposure for difference countries for each of the respective concomitant AED subgroups.

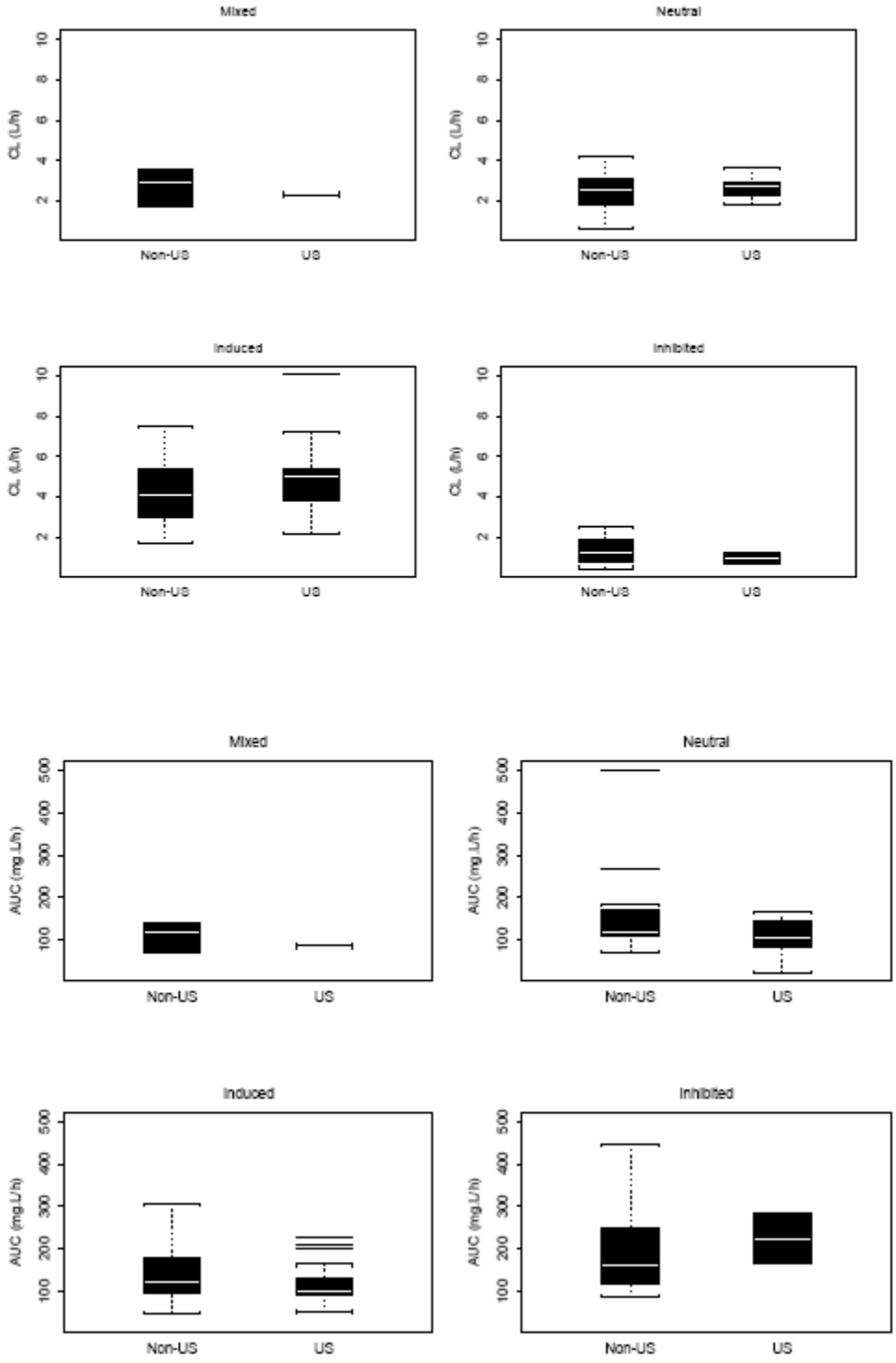
- Lamotrigine clearance is decreased in patients on "inhibiting" drugs such as VPA, is increased on EIAEDs, and is intermediate between both groups for patients on "neutral" AEDs or VPA and EIAEDs. From another perspective, levels are quite similar (as might be expected) in patients one VPA and EIAEDs or "neutral" AEDs as concomitant treatment. The magnitude of the effect of VPA to increase levels is thought to be similar to the magnitude of the effect of EIAEDs to lower lamotrigine levels.

- Of interest, lamotrigine clearance is similar for patients treated with "neutral" AEDs or VPA plus an EIAED. Considering that the opposing effects of VPA and EIAEDs are of a similar magnitude, one might expect that these effects would cancel each other out and that results would be the same as those for patients who were taking concomitant AEDs (e.g., "neutral" AEDs) that were not expected to alter lamotrigine clearance.

- Lamotrigine exposure (AUC) is increased in patients on "inhibiting" drugs such as VPA, is decreased on EIAEDs, and is intermediate between both groups for patients on "neutral" AEDs or VPA and EIAEDs.

- Of interest, lamotrigine exposure (AUC) is similar for patients treated with "neutral" AEDs or VPA plus an EIAED. Considering that the opposing effects of VPA and EIAEDs are of a similar magnitude, one might expect that these effects would cancel each other out and that results would be the same as those for patients who were taking concomitant AEDs (e.g., "neutral" AEDs) that were not expected to alter lamotrigine clearance.

Figure 11-20: Box-Plot Summary of Posthoc Estimates of Lamotrigine Oral Clearance (CL/F(L/h)) and AUC (mg.h/L) versus Region by AED co-medication (Induced, Inhibited, Neutral and Mixed)



Reviewer Comment :

- Figure 11-20 suggests that there is no major/clear difference of lamotrigine clearance or AUC exposure for U.S. patients vs non-U.S. patients for each of the respective concomitant AED subgroups. The following comments are similar to those noted above for figure 11-19 in comparing results of individual countries.

- Lamotrigine clearance is decreased in patients on "inhibiting" drugs such as VPA, is increased on EIAEDs, and is intermediate between both groups for patients on "neutral" AEDs or VPA and EIAEDs.

- Of interest, lamotrigine clearance is similar for patients treated with "neutral" AEDs or VPA plus an EIAED. Considering that the opposing effects of VPA and EIAEDs are of a similar magnitude, one might expect that these effects would cancel each other out and that results would be the same as those for patients who were taking concomitant AEDs (e.g., "neutral" AEDs) that were not expected to alter lamotrigine clearance.

- Lamotrigine exposure (AUC) is increased in patients on "inhibiting" drugs such as VPA, is decreased on EIAEDs, and is intermediate between both groups for patients on "neutral" AEDs or VPA and EIAEDs.

- Of interest, lamotrigine exposure (AUC) is similar for patients treated with "neutral" AEDs or VPA plus an EIAED. Considering that the opposing effects of VPA and EIAEDs are of a similar magnitude, one might expect that these effects would cancel each other out and that results would be the same as those for patients who were taking concomitant AEDs (e.g., "neutral" AEDs) that were not expected to alter lamotrigine clearance.

SPONSOR'S EVALUATION OF THE EXPOSURE RESPONSE RELATIONSHIP BY REGION

Pharmacokinetic Endpoint Used in the Exposure Response Analysis

The PK profile of lamotrigine XR at steady-state is flat, due to the slow apparent rate of absorption and relatively slow clearance. As such, any concentration prediction during the dosing interval or over the maintenance period is appropriate to estimate the relationship between seizure frequency and lamotrigine serum concentrations. The individual predicted concentration at the end of the maintenance period was derived from the final population PK model parameter estimates on the day of the final frequency recording (timed at 00:00), dosing history and covariates (i.e. covariates in the population PK model (AED therapy and body weight)). A total of 202 subjects were included in the exposure-response data set. Subjects were excluded either because of missing baseline values, or because they did not complete the treatment phase. No last observation carried forward (LOCF) analysis was performed in any of the PK-PD evaluations.

One subject, Subject 22 (14 years old) had very high predicted lamotrigine concentrations. The dose regimen of lamotrigine for Subject 22 was similar to all other subjects. However, this subject had the lowest weight (24 kg) compared to equivalent subjects (U.S., valproic acid co-medication) (46 to 122

kg). The original final model was re-fitted with this subject excluded. Decreases in the inter-individual variability on CL, and the residual error variance terms was seen when subject 22 was excluded. Therefore, **Subject 22 was excluded from any subsequent analysis.**

RESULTS OF PHARMACOKINETIC EVALUATION BY REGION

A total of 412 serum concentrations from 100 subjects were included in the population PK analysis. The reason for exclusion of data included missing or incomplete sample concentration/dose records.

In addition, five concentrations which had the time after dose greater than 48 hours were excluded prior to the population PK analysis. Given the trial design and protocol sampling schedule, the sampling times for these data were deemed questionable.

Summary of the Administered Daily Lamotrigine -XR Dose by Region in the Pharmacokinetic Data Set

Histograms of the overall total daily lamotrigine XR dose profile for subjects in the PK data set, at the start of the titration phase and on the day of the final frequency recording are presented. Overall, comparable dose ranges were achieved by visit 6 (maintenance period) between the two regions. Table 6-1 and Table 6-2 below, present the number of subjects receiving induced, inhibited, mixed and neutral concomitant AEDs at visit 6 (maintenance period). The majority of subjects received 500 mg in the induced group, 200 mg in the inhibited group and 300 mg in the mixed group for both the U.S. and non-U.S. subjects.

Table 6-1: Summary of U.S. Subjects receiving AEDs

Dose (mg)	Number of Subjects Receiving Concomitant AED			
	Induced	Inhibited	Mixed	Neutral
50	0	0	0	1
200	0	3	1	0
300	1	0	0	11
400	1	0	0	0
450	1	0	0	1
500	14	0	0	0

Table 6-2: Summary of non-U.S. Subjects receiving AEDs

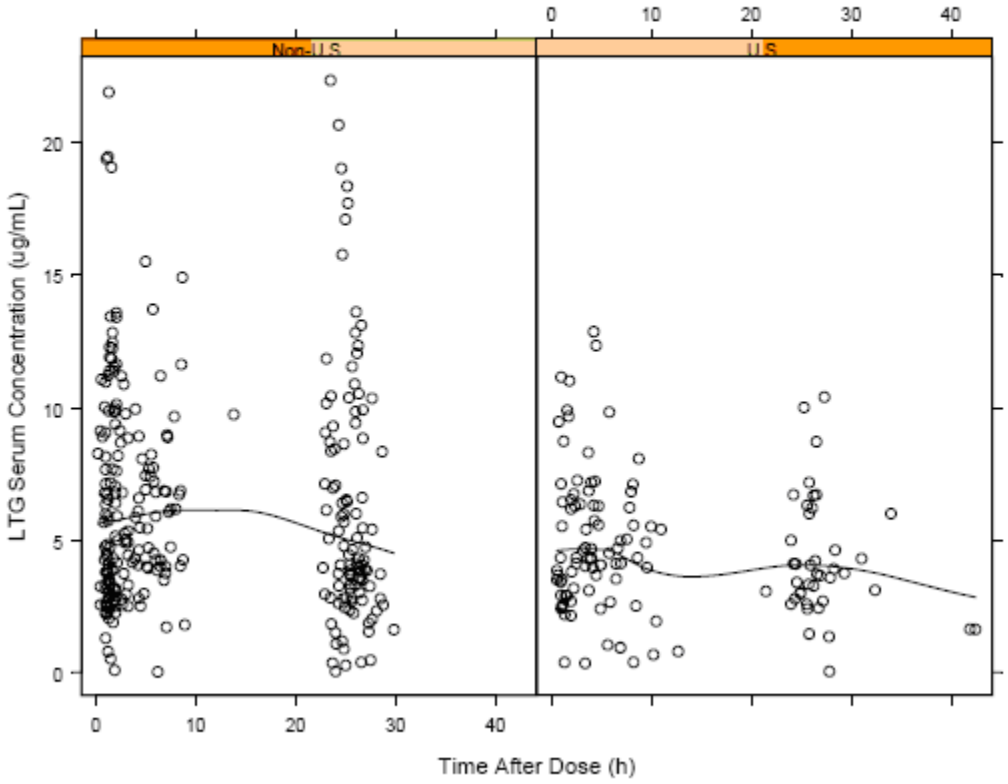
Dose (mg)	Number of Subjects Receiving Concomitant AED			
	Induced	Inhibited	Mixed	Neutral
162.5	0	1	0	0
200	0	13	1	0
212.5	0	0	1	0
250	0	3	0	0
300	1	0	0	11
400	2	0	0	1
500	22	0	1	0
550	1	0	0	0
600	6	0	0	0

Subjects 1804 and 1840 terminated following visit 5 and are not included in table above

Summary of Serum Lamotrigine Concentration Data by Region

Summary plots of lamotrigine serum concentration data versus time after dose, by region (U.S. versus non-U.S.) is presented in Figure 11-5 and by AED group (Inhibited, Induced, Neutral and Mixed) and region in Figure 11-6.

Figure 11-5: Summary Plot of Lamotrigine Serum Concentrations (µg/mL) versus Time After Dose by Region (U.S. versus non-U.S.)



The solid line represents the local regression (Loess) smoothing line.

Lamotrigine concentration data for one pediatric patient, subject 22 are provided below.

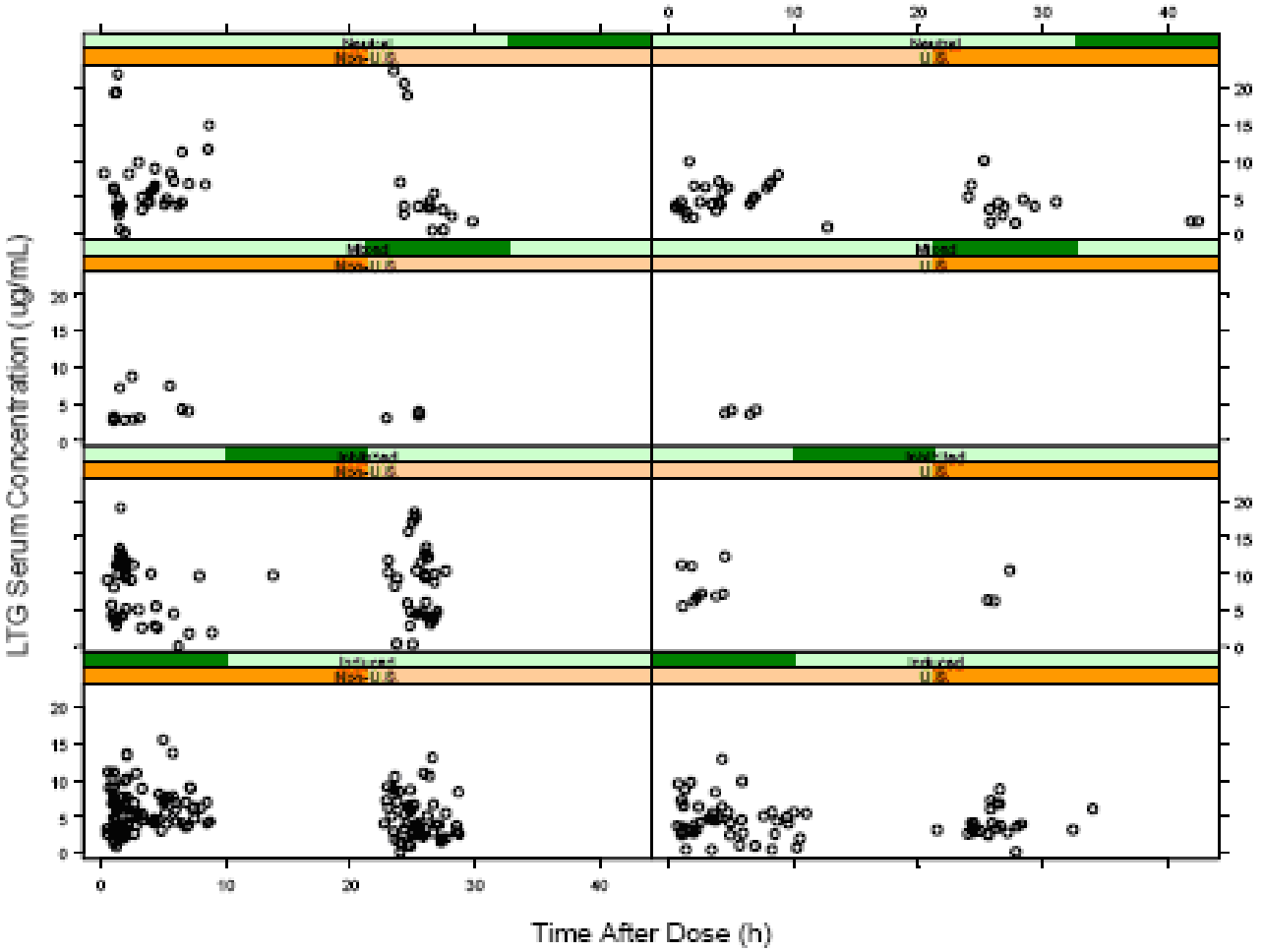
ID	CENT	DOSE	TRT	NDAY	DATE	TIME	TIME AFTER DOSE (h)	LTG CONC (ug/mL)
(b) (4)								

Reviewer Comment :

- These data show that lamotrigine concentration at PK steady state in an individual patient can show substantial excursions at various times over the dosing interval. These data

appear to conflict with the sponsor's argument that serum lamotrigine concentrations are relatively constant at PK steady state because clearance counteracts the increase in lamotrigine level after administration and absorption.

Figure 11-6: Summary Plot of Lamotrigine Serum Concentrations (µg/mL) versus Time After Dose by Region (U.S. versus non-U.S.) and AED co-medication (Induced, Inhibited, Neutral and Mixed)

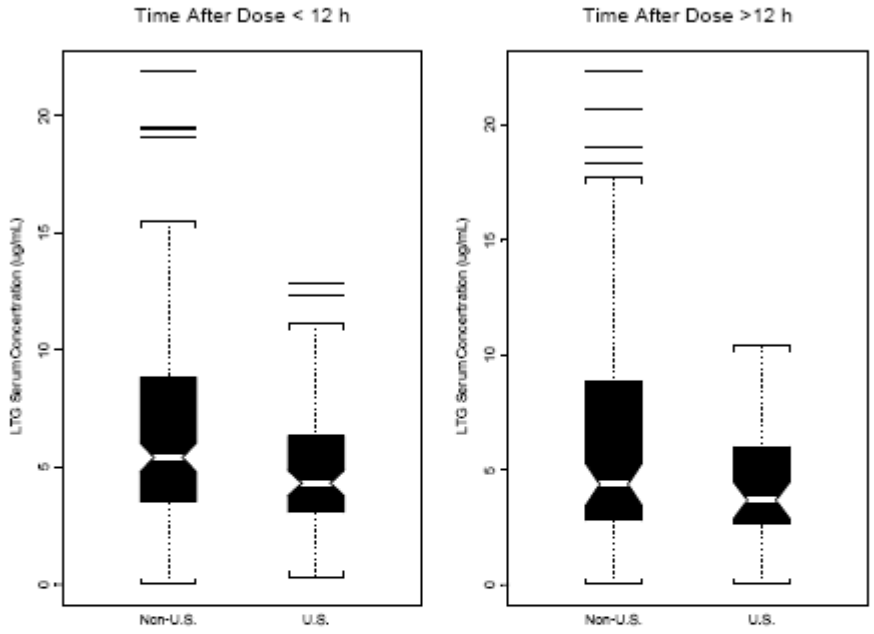


Reviewer Comment :

These results suggest that the populations do not show major differences in the range of serum lamotrigine concentrations within several hours after dosing (e.g., ~ 1-9) vs many hours after dosing (~ 24-30 hrs). However, the sponsor did not show that levels in individuals do not show much variation. Also it is not absolutely clear to me that patients sampled after 24 hours have not received another dose at around 24 hours after the first dose. If true these analyses would not be very meaningful.

A box-plot summary by region and time after dose <12 h and >12h, with supporting statistics is presented in Figure 6-1 below.

Figure 6-1: Box Plot of Lamotrigine Serum Concentrations (µg/mL) versus Time After Dose by Region (U.S. versus non-U.S.)

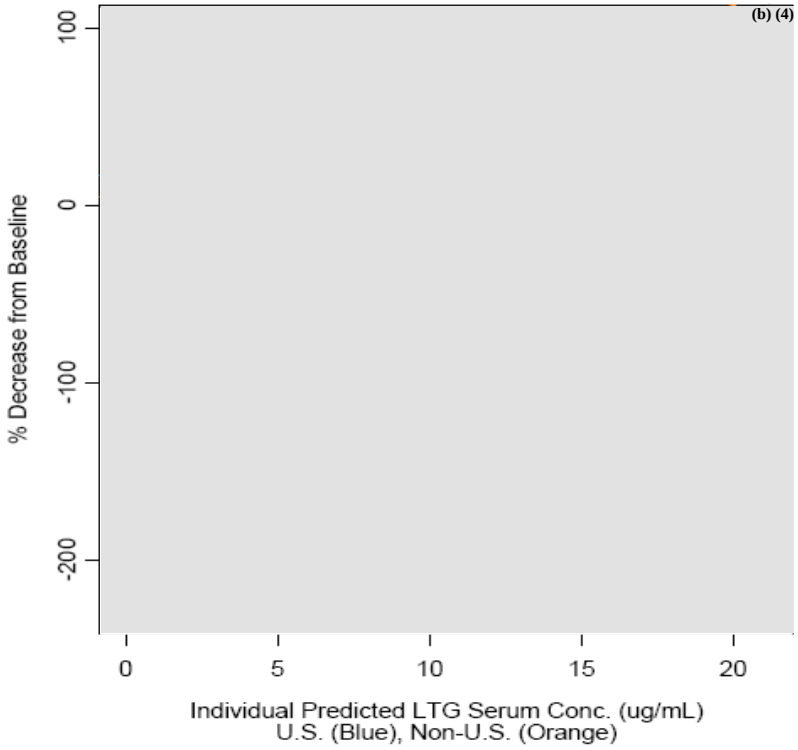


	Time <12 h post-dose		*Time > 12h post- dose*	
	Non-U.S.	**U.S.**	**Non-U.S.**	**U.S.**
N	177	87	106	42
Median	5.43	4.33	4.37	3.68
25th Percentile	3.54	3.13	2.85	2.71
75th Percentile	8.84	6.33	8.81	5.74
95% Confidence Limits of Mean	(5.82, 6.98)	(4.35, 5.49)	(5.28, 7.10)	(3.43, 4.87)

From the graphical evaluation, it can clearly be seen that within each AED group there were no gross differences in lamotrigine serum concentration between U.S. and non-U.S. subjects during the maintenance phase that are likely to explain differences in the exposure response evaluation as a result of a higher concentration range in non-U.S. subjects. Similar median and inter-quartile ranges (25^{th} and 75^{th} percentiles) are observed for both time windows (time after dose <12 h and time after dose > 12 h) as summarized in Figure 6-1 with summary statistics.

The sponsor also conducted exposure-response plots for individual patients showing their % seizure rate decrease/reduction from baseline (at the final visit) relative to the serum lamotrigine concentration for U.S. vs non-U.S. patients. The following figure shows these results for all treatments.

% Decrease in Seizure Frequency from Baseline (All patients : from sponsor's report and also U.S. vs non-U.S. patients)



Reviewer Comment :

- This plot showing the exposure-response for U.S. vs non-U.S. patients incorporates placebo results ("0" serum lamotrigine concentration). The use of placebo results facilitates the demonstration of a positive slope for each population but the slope is greater for non-U.S. patients. These analyses suggests that there is an effect of XR lamotrigine (vs placebo) for both subgroup although the slope is greater for the non-U.S. patients (vs the U.S. patients).

- There is no clearly defined positive slope for the exposure-response analyses without placebo because the "slopes" appear to be relatively flat/horizontal and do not clearly suggest a concentration response. If there is a positive slope, it would seem to be quite shallow.

Sponsor Conclusions

Pharmacokinetics

- Comparable dose ranges during the maintenance period were achieved in U.S. and non-U.S. subjects.

- The serum lamotrigine concentration ranges observed within each AED therapy group during the maintenance phase were generally similar in U.S. and non-U.S. subjects.

- The serum lamotrigine concentration concentrations in subjects receiving enzyme inhibitors were generally higher than those observed in other AED therapy groups (mixed, neutral or induced)

- Region as a covariate on oral clearance was not considered statistically or clinically significant.

- Any difference in the efficacy of lamotrigine XR in U.S. and non-U.S. subjects is unlikely to be as a consequence of differences in PK and resulting serum concentrations in LAM100034 observed in the two groups.

Exposure-Response

- The concentration-response analysis of seizure frequency (baseline and on treatment) did not determine a regional difference.

- Concentration-response analysis of partial seizure frequency data using the percent decrease from baseline did not determine regional differences on either placebo or concentration-effect.

- Concentration-response analysis via logistic regression showed a clear relationship between the probability of a response with concentration; however, this was independent of region.

Reviewer Comment :

- In general, I agree with the sponsor's conclusions. However, I think that exposure-response curve for non-U.S. patients was greater (e.g., greater slope) than that for the U.S. patients and these results that include placebo response for each respective group also seem likely because of the higher placebo "responses" of U.S. patients.

FDA Pharmacometric/Clinical Pharmacology Review

(Reviewers : Joo Yeon Lee, Ph.D., and Sripal Mada, Ph.D.; Secondary Reviewer : Hao Zhu, Ph.D.) (See this review for details)

Executive Summary

The sponsor is seeking the market approval for lamotrigine XR for the treatment of epilepsy in subjects with partial seizures. The original submission was sent to the FDA on November 22, 2006. In the approvable letter issued on September 21, 2007, the agency expressed concerns about the discrepancy of the median percentage changes from baseline between the U.S. and non-U.S. sites in the pivotal trial (Study LAM100034). In the approvable letter, the agency requested additional analyses to compare the exposure-response relationships between the U.S. and non-U.S. sites. In response to the agency's request, the sponsor performed additional exposure-response analysis in the current submission.

In addition to the exposure response analysis for the US / non US sites, the sponsor also submitted results of a pivotal single-dose randomized, parallel-group, open-label study to demonstrate bioequivalence of 300 mg lamotrigine XR relative to 100 mg + 200 mg lamotrigine XR and to demonstrate the effect of food on 300 mg lamotrigine XR in healthy male and female volunteers. This study has no relevance for this current submission, (b) (4)

After reviewing the sponsor's submission, we found:

- No statistically significant different exposure-response relationships between the U.S. and non-U.S. sites could be identified from both the sponsor's and the reviewer's analyses.

- The discrepancy of the median percentage changes from baseline between the U.S. and non-U.S. sites in the pivotal trial (Study LAM100034) appear to be associated with different lamotrigine exposure levels, with slightly higher plasma concentrations being observed in patients from the non-U.S. sites than from the U.S. sites. Higher lamotrigine concentrations in the patients from the non-U.S sites appears to be related to the larger proportion of subjects receiving valproic acid (an enzyme inhibitor) in the non-U.S sites (26.6% (17/64) from the non-U.S sites vs. 8.8% (3/34) from the U.S sites).
- The result of the bioequivalence study showed that a 300 mg lamotrigine XR is bioequivalent to combination of 100 mg + 200 mg lamotrigine XR tablets and there is no significance of food on the 300 mg lamotrigine XR tablets.

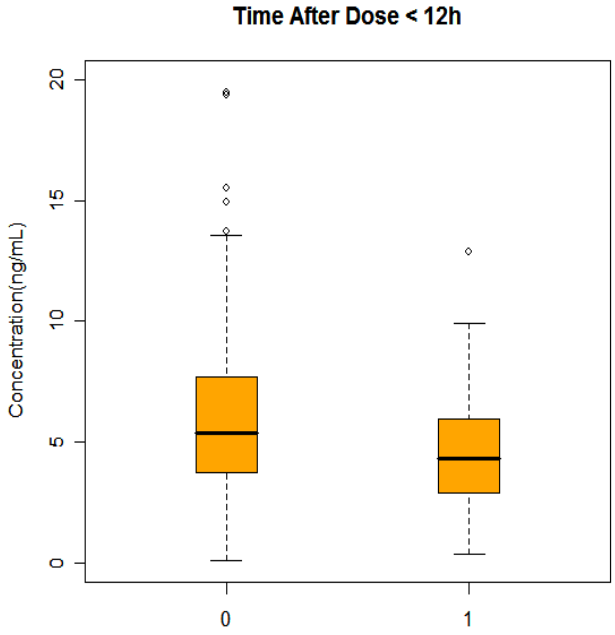
Recommendations

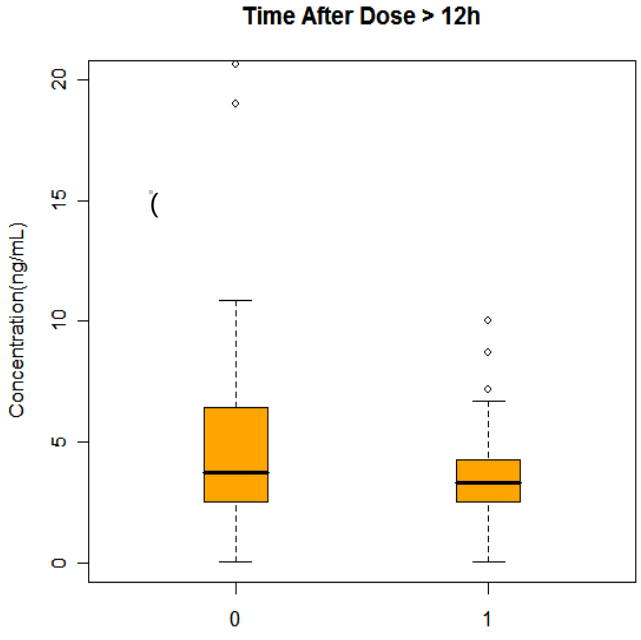
The Office of Clinical Pharmacology has reviewed the present submission (NDA 22115). We concluded that the difference in effectiveness between the U.S. and non-U.S. sites, as measured by percentage change from baseline, is likely due to the difference in lamotrigine exposure levels between the U.S. and non-U.S. sites, not due to the response difference.

Additional Explorations by Pharmacometrics Team

The following exploratory analyses were conducted by the Pharmacometrics Team after discussions with this clinical reviewer. Although the Pharmacometrics Team had initially suggested that the difference in responses between U.S. and non-U.S. patients may have been related to higher lamotrigine exposures of non-U.S. patients, perhaps because of the higher proportion of non-U.S. patients taking concomitant VPA and experiencing higher lamotrigine levels. Because my exploratory efficacy analyses had suggested that the increased response also occurred in non-U.S. patients (vs. similar U.S. patients) who had not been treated with any concomitant AED, my discussions with the Pharmacometrics Team revolved around this issue. Consequently, additional analyses were performed to explore analyses in patients who had not received any concomitant VPA.

Concentrations of Lamotrigine in US vs Non-US Patients Treated with Concomitant AEDs Excluding VPA

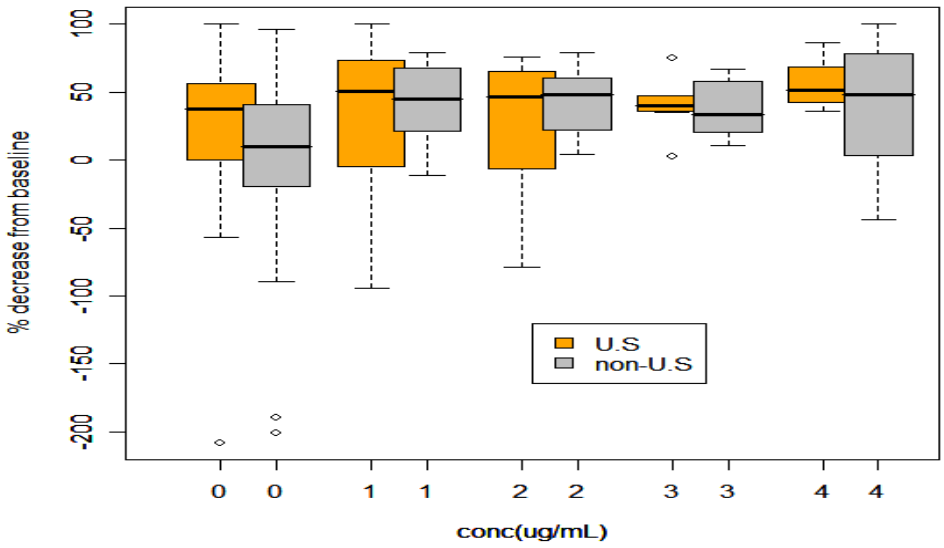




Reviewer Comment :

- These analyses excluding results of patients treated with any concomitant VPA were comprised of a substantial number of patients in each subgroup (U.S., and non-U.S.). Although serum lamotrigine levels (< 12 hours after dosing) were slightly higher in non-U.S. patients, later levels (> 12 hours after dosing) were very similar. Overall, serum lamotrigine levels were quite similar in these subgroups and did not support the view that increased lamotrigine levels in non-U.S. patients because of greater concomitant VPA use was mainly responsible for the difference in treatment difference in non-U.S. vs U.S. patients.

% Decrease (from Baseline) in Seizure Frequency for Placebo ("0" concentration lamotrigine) and Lamotrigine XR – Treated Patients (US vs Non-US Patients) According to Lamotrigine Concentration Quartiles in Patients on Concomitant AEDs Excluding VPA



Reviewer Comment :

- It is noteworthy that serum lamotrigine levels in U.S. vs non-U.S. patients are quite similar for each of the quartiles of lamotrigine levels and that the levels do not appear to show an increased response as levels increase from the lowest quartile to the highest quartile.

- These results (derived from patients who did not have any potentially confounding influence of VPA) that do not suggest a concentration-exposure response, do not support the view that increasing concentrations are associated with increased efficacy responses. If this is true, then the shape of the dose and concentration responses is not known. This possibility could suggest that patients may be treated with excessive lamotrigine that may be increasing the risk for adverse reactions.

- **I fully recognize that these data are not ideal because patients have not been randomized to different XR lamotrigine doses or achieving different lamotrigine concentrations. Nevertheless, I think that these results are consistent and supportive of the possibility that there is no clear dose-response or concentration-response relationships for the XR lamotrigine lamotrigine dosing regimens that have been used.**

Median and Mean % Decrease from Baseline in Seizure Frequency for Placebo- and XR Lamotrigine- Treated Patients (Excluding All Patients with Any Concomitant VPA Use) According to Subgroups (U.S. vs non-U.S.)

		Median	Mean
PLACEBO	U.S	37%	22%
	Non U.S	10%	-3%
LAMOTRIGINE	U.S	47%	37%
	Non U.S	48%	40%

Reviewer Comment :

- These data provided by the pharmacometrics team also supports the possibility that the diminished treatment effect/difference of XR lamotrigine in U.S. patients may have primarily been related to the large placebo "response" in U.S. patients.

- Overall, the additional exploratory analyses conducted by the Pharmacometrics Team supports the view that the large and "excessive" placebo response of U.S. patients was probably the major reason for the markedly diminished treatment difference of U.S. patients vs non-U.S. patients.

Revised/Updated Modal Daily Dosing Based Upon Concomitant AED in Study 34

The sponsor submitted a revised, updated table of modal dosing data following its inspections. There were small differences compared to the previous summary table before all the inspections.

Summary of XR Lamotrigine Modal Daily dosing for Study LAM100034 (Population: Safety*)
(This table was revised and updated by the sponsor based upon the inspections of all sites)

Dose (mg/day)	Lamictal-XR VPA "alone" (or with "neutral AEDs) (N=24)	Lamictal-XR VPA with EIAEDs (N=7)	Lamictal-XR EIAEDs (N=60)	Lamictal-XR All other regimens (N=27)	Lamictal-XR ALL (N=118)
12.5	2	0	0	0	2
25	2	1	0	0	3
50	0	0	5	2	7
100	0	0	2	1	3
150	1	0	0	0	1
200	17	4	0	0	21
250	2	0	0	0	2
300	0	0	0	23	23
400	0	0	3	1	4
450	0	0	2	0	2
500	0	1	42	0	43
600	0	1	6	0	7

* **Updated results subsequent to Sponsor reinspections of all study sites**

Reviewer Comment :

- These data support a recommended daily dose of :
    - 200-250 mg for VPA alone or VPA with "neutral" AED(s)
    - 200-250 mg for VPA with EIAED(s); The patient with the modal dose of 25 mg daily achieved a 200 mg dose but discontinued prematurely and because of this the modal calculation indicated a 25 mg modal dose. Two patients had much higher modal doses of 500 and 600 mg. Of interest, patients in this category generally showed serum lamotrigine levels and PK clearance values that were similar to those of patients in the "neutral" AED category who have a higher recommended daily dose of 300-400 mg. This empirical observation is theoretically what would be expected

based upon the fact that the magnitude of the effect of VPA for increasing levels and EIAED for decreasing levels is quantitatively similar.

- 300-400 mg for "neutral" AED(s)
- 400-600 mg for EIAED(s)

Additional Vital Signs Analyses

FDA Comment:
"We have requests for additional analyses of vital signs (VS). In Study 34, you conducted all analyses assessing effects of treatment using the single set of VS data at the last visit immediately prior to randomization and initiation of treatment as the baseline comparator. In conducting these analyses, you did not include VS data from other, earlier pre-treatment visits (e.g. at least 2 more). We believe that including all pre-treatment VS in the calculation of the "baseline" value by averaging all pre-treatment VS data will potentially provide a better assessment of the baseline VS than a single set of VS data. A single set of VS data may not necessarily be a good reflection of the "true" or average VS for an individual patient for use as a comparator to multiple sets of VS measurements after treatment.

We therefore request the following analyses be conducted for all VS data in Study 34 using all pre-treatment VS and averaging all these results for each parameter for each patient and comparing this "baseline" to all the post-treatment measurements at each visit. Please submit the analyses over time for:

1) Mean absolute data for SBP, DBP, and pulse.

2) Change from baseline for each VS parameter.

3) Outlier results of potential clinical concern using the threshold criteria that we previously provided to you

4) A data listing of all patients with any outlier result. Outlier analyses should be presented as in the attached/appended table (as previously requested from GSK)."

GSK Response:
The requested analyses are provided in the Vital Signs Analyses Document. No clinically relevant findings were identified in these tables.

Table V.3
Incidence of Change from Baseline Outliers for Systolic BP, Diastolic BP, and Pulse
at Various Time Perspectives in DBP Study 100034

Vital Sign	Treatment	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
SBP Inc>=20	LTG	2/111 (2%)	5/105 (5%)	2/ 98 (2%)	3/ 97 (3%)	6/108 (6%)
SBP Inc>=20	Placebo	7/119 (6%)	6/117 (5%)	6/111 (5%)	3/108 (3%)	3/114 (3%)
SBP Inc>=20	Rx Effect	-4%	-0%	-3%	0%	3%
SBP Inc>=40	LTG	0/111 (0%)	0/105 (0%)	1/ 98 (1%)	0/ 97 (0%)	0/108 (0%)
SBP Inc>=40	Placebo	1/119 (<1%)	0/117 (0%)	1/111 (<1%)	1/108 (<1%)	0/114 (0%)
SBP Inc>=40	Rx Effect	-1%	0%	0%	-1%	0%
DBP Inc>=10	LTG	14/111 (13%)	16/105 (15%)	9/ 98 (9%)	7/ 97 (7%)	14/108 (13%)
DBP Inc>=10	Placebo	15/119 (13%)	7/117 (6%)	14/111 (13%)	15/108 (14%)	5/114 (4%)
DBP Inc>=10	Rx Effect	0%	9%	-3%	-7%	9%
DBP Inc>=20	LTG	2/111 (2%)	2/105 (2%)	1/ 98 (1%)	2/ 97 (2%)	2/108 (2%)
DBP Inc>=20	Placebo	1/119 (<1%)	2/117 (2%)	0/111 (0%)	2/108 (2%)	0/114 (0%)
DBP Inc>=20	Rx Effect	1%	0%	1%	0%	2%
SBP Dec<=20	LTG	4/111 (4%)	2/105 (2%)	4/ 98 (4%)	8/ 97 (8%)	4/108 (4%)
SBP Dec<=20	Placebo	4/119 (3%)	8/117 (7%)	7/111 (6%)	10/108 (9%)	6/114 (5%)
SBP Dec<=20	Rx Effect	0%	-5%	-2%	-1%	-2%
SBP Dec<=40	LTG	0/111 (0%)	0/105 (0%)	0/ 98 (0%)	1/ 97 (1%)	0/108 (0%)
SBP Dec<=40	Placebo	0/119 (0%)	1/117 (<1%)	1/111 (<1%)	1/108 (<1%)	1/114 (<1%)
SBP Dec<=40	Rx Effect	0%	-1%	-1%	0%	-1%
DBP Dec<=10	LTG	15/111 (14%)	11/105 (10%)	12/ 98 (12%)	18/ 97 (19%)	17/108 (16%)
DBP Dec<=10	Placebo	11/119 (9%)	20/117 (17%)	17/111 (15%)	21/108 (19%)	18/114 (16%)
DBP Dec<=10	Rx Effect	4%	-7%	-3%	-1%	-0%
DBP Dec<=20	LTG	1/111 (<1%)	0/105 (0%)	0/ 98 (0%)	2/ 97 (2%)	1/108 (<1%)
DBP Dec<=20	Placebo	0/119 (0%)	4/117 (3%)	4/111 (4%)	3/108 (3%)	3/114 (3%)
DBP Dec<=20	Rx Effect	1%	-3%	-4%	-1%	-2%
Pulse Inc>=15	LTG	6/112 (5%)	8/106 (8%)	9/ 99 (9%)	5/ 98 (5%)	9/109 (8%)
Pulse Inc>=15	Placebo	2/119 (2%)	11/117 (9%)	7/111 (6%)	9/108 (8%)	4/114 (4%)
Pulse Inc>=15	Rx Effect	4%	-2%	3%	-3%	5%
Pulse Inc>=30	LTG	0/112 (0%)	0/106 (0%)	3/ 99 (3%)	2/ 98 (2%)	0/109 (0%)
Pulse Inc>=30	Placebo	0/119 (0%)	1/117 (<1%)	2/111 (2%)	1/108 (<1%)	0/114 (0%)
Pulse Inc>=30	Rx Effect	0%	-1%	1%	1%	0%
Pulse Dec<=15	LTG	3/112 (3%)	2/106 (2%)	5/ 99 (5%)	3/ 98 (3%)	4/109 (4%)
Pulse Dec<=15	Placebo	4/119 (3%)	4/117 (3%)	5/111 (5%)	3/108 (3%)	4/114 (4%)
Pulse Dec<=15	Rx Effect	-1%	-2%	1%	0%	0%
Pulse Dec<=30	LTG	0/112 (0%)	0/106 (0%)	0/ 99 (0%)	0/ 98 (0%)	0/109 (0%)
Pulse Dec<=30	Placebo	0/119 (0%)	0/117 (0%)	0/111 (0%)	0/108 (0%)	0/114 (0%)
Pulse Dec<=30	Rx Effect	0%	0%	0%	0%	0%

LTG = Lamotrigine; Rx Effect (LTG% - Placebo%)
Systolic Blood Pressure and Diastolic Blood Pressure were measured in mmHg; Pulse was measured in BPM.
Baseline for each patient was the average of all vital sign measurements in the screen and baseline phase.
Titration = occurring during titration period. Maintenance = occurring during maintenance period.
Persisting = occurring during titration period and persisting into maintenance period.
Whole study = occurring at any time during titration and/or maintenance period.
Outlier vital signs assessed after the end of double blind treatment are not included in the Titration, Maintenance, or the Whole Study columns. However, these visits are included in the by-visit columns on the recorded treatment visit number.

Table V.3
Incidence of Change from Baseline Outliers for Systolic BP, Diastolic BP, and Pulse at Various Time Perspectives in DBP Study 100034

Vital Sign	Treatment	Titration	Maintenance	Persisting	Whole Study
SBP Inc>=20	LTG	4/113 (4%)	9/107 (8%)	1/107 (<1%)	12/113 (11%)
SBP Inc>=20	Placebo	9/120 (8%)	12/115 (10%)	3/115 (3%)	15/120 (13%)
SBP Inc>=20	Rx Effect	-4%	-2%	-2%	-2%
SBP Inc>=40	LTG	0/113 (0%)	1/107 (<1%)	0/107 (0%)	1/113 (<1%)
SBP Inc>=40	Placebo	1/120 (<1%)	2/115 (2%)	0/115 (0%)	3/120 (3%)
SBP Inc>=40	Rx Effect	-1%	-1%	0%	-2%
DBP Inc>=10	LTG	23/113 (20%)	20/107 (19%)	4/107 (4%)	36/113 (32%)
DBP Inc>=10	Placebo	15/120 (13%)	27/115 (23%)	2/115 (2%)	36/120 (30%)
DBP Inc>=10	Rx Effect	8%	-5%	2%	2%
DBP Inc>=20	LTG	2/113 (2%)	4/107 (4%)	1/107 (<1%)	5/113 (4%)
DBP Inc>=20	Placebo	1/120 (<1%)	4/115 (3%)	0/115 (0%)	5/120 (4%)
DBP Inc>=20	Rx Effect	1%	0%	1%	0%
SBP Dec<=20	LTG	6/113 (5%)	12/107 (11%)	1/107 (<1%)	15/113 (13%)
SBP Dec<=20	Placebo	7/120 (6%)	15/115 (13%)	2/115 (2%)	17/120 (14%)
SBP Dec<=20	Rx Effect	-1%	-2%	-1%	-1%
SBP Dec<=40	LTG	0/113 (0%)	1/107 (<1%)	0/107 (0%)	1/113 (<1%)
SBP Dec<=40	Placebo	0/120 (0%)	1/115 (<1%)	0/115 (0%)	1/120 (<1%)
SBP Dec<=40	Rx Effect	0%	0%	0%	0%
DBP Dec<=10	LTG	21/113 (19%)	29/107 (27%)	4/107 (4%)	38/113 (34%)
DBP Dec<=10	Placebo	16/120 (13%)	37/115 (32%)	7/115 (6%)	44/120 (37%)
DBP Dec<=10	Rx Effect	5%	-5%	-2%	-3%
DBP Dec<=20	LTG	1/113 (<1%)	2/107 (2%)	0/107 (0%)	3/113 (3%)
DBP Dec<=20	Placebo	1/120 (<1%)	7/115 (6%)	0/115 (0%)	8/120 (7%)
DBP Dec<=20	Rx Effect	0%	-4%	0%	-4%
Pulse Inc>=15	LTG	9/114 (8%)	18/108 (17%)	2/108 (2%)	22/114 (19%)
Pulse Inc>=15	Placebo	7/120 (6%)	15/115 (13%)	1/115 (<1%)	21/120 (18%)
Pulse Inc>=15	Rx Effect	2%	4%	1%	2%
Pulse Inc>=30	LTG	0/114 (0%)	5/108 (5%)	0/108 (0%)	5/114 (4%)
Pulse Inc>=30	Placebo	0/120 (0%)	4/115 (3%)	0/115 (0%)	4/120 (3%)
Pulse Inc>=30	Rx Effect	0%	1%	0%	1%
Pulse Dec<=15	LTG	5/114 (4%)	7/108 (6%)	2/108 (2%)	8/114 (7%)
Pulse Dec<=15	Placebo	7/120 (6%)	8/115 (7%)	1/115 (<1%)	12/120 (10%)
Pulse Dec<=15	Rx Effect	-1%	-0%	1%	-3%
Pulse Dec<=30	LTG	0/114 (0%)	0/108 (0%)	0/108 (0%)	0/114 (0%)
Pulse Dec<=30	Placebo	0/120 (0%)	0/115 (0%)	0/115 (0%)	0/120 (0%)
Pulse Dec<=30	Rx Effect	0%	0%	0%	0%

LTG = Lamotrigine; Rx Effect (LTG% - Placebo%)
Systolic Blood Pressure and Diastolic Blood Pressure were measured in mmHg; Pulse was measured in BPM.
Baseline for each patient was the average of all vital sign measurements in the screen and baseline phase.
Titration = occurring during titration period. Maintenance = occurring during maintenance period.
Persisting = occurring during titration period and persisting into maintenance period.
Whole study = occurring at any time during titration and/or maintenance period.
Outlier vital signs assessed after the end of double blind treatment are not included in the Titration, Maintenance, or the Whole Study columns. However, these visits are included in the by-visit columns on the recorded treatment visit number.

Reviewer Comment :

- I agree that there is no clear effect of lamotrigine on vital signs but there are some suggestions of at least transient modest increments in diastolic blood pressure, especially in the titration period.

The sponsor had also been asked (subsequent to the Approvable letter) to conduct detailed analyses of orthostatic (supine and standing) VS collected in healthy volunteers in a Thorough QTc Study (SCA104648). The sponsor submitted these requested analyses prior to the submission of its Complete Response to the Approvable letter. However, I have reviewed these results and have chosen to describe them briefly here. The study design of this study is outlined here in this table.

Treatment administration:

Session	Treatment group 1		Treatment group 2
Session 1	Day 1: Moxifloxacin 400 mg or moxifloxacin placebo (ECG/PK)		Day 1: Moxifloxacin or moxifloxacin placebo (ECG/PK)
Session 2	Day 1: Moxifloxacin 400 mg or moxifloxacin placebo (ECG/PK)		Day 1: Moxifloxacin or moxifloxacin placebo (ECG/PK)
Session 3	Lamotrigine: Days 1–14: 25 mg Days 15–28: 50 mg Days 29–41:100 mg Day 42: 100 mg (ECG/PK)	Dosage instructions: 1 × 25 mg am once daily 1 × 25 mg am; 1 × 25 mg pm 2 × 25 mg am; 2 × 25 mg pm 2 × 25 mg am; 2 × 25 mg pm	Days 1–42: lamotrigine placebo Day 42: lamotrigine placebo (ECG/PK)
Session 4	Lamotrigine: Day 43–49: 200 mg Day 50–62: 300 mg Day 63: 300 mg (ECG/PK)	 1 × 100 mg am; 1100 mg pm 1 × 100 mg + 2 × 25 mg am; 1 × 100 mg + 2 × 25 mg pm 1 × 100 mg + 2 × 25 mg am; 1 × 100 mg + 2 × 25 mg pm	 Days 43–62: lamotrigine placebo Day 63: lamotrigine placebo (ECG/PK)
Session 5	Lamotrigine: Day 64–76: 400 mg Day 77: 400 mg (ECG/PK)	 2 × 100 mg am; 2 × 100 mg pm 2 × 100 mg am; 2 × 100 mg pm	 Days 64–76: lamotrigine placebo Day 77: lamotrigine placebo (ECG/PK)
Down–titration	Lamotrigine: Day 78–79: 300 mg Day 80–81: 200 mg Day 82–83: 100 mg Days 84–85: 50 mg	 1 × 100 mg + 2 × 25 mg am; 1 × 100 mg + 2 × 25 mg pm 1 × 100 mg am; 1 × 100 mg pm 2 × 25 mg am; 2 × 25 mg pm 1 × 25 mg am; 1 × 25 mg pm	 Days 78–85: lamotrigine placebo

In this study, patients were randomized to either placebo or immediate-release lamotrigine. Patients randomized to lamotrigine were titrated to 3 different doses (100, 300, and 400 mg) and were studied at days 42, 63, and 77 after achieving PK steady state at each dose. Patients had ECGs and orthostatic VS collected at similar times (pre-dosing and + 2, 8, and 22-24 hours after dosing. However, in this study, potential effects of lamotrigine on orthostatic VS were confounded by dose and time because it was not possible to assess and compare effects of different doses at the same time after similar treatment durations.

Based upon DNP requests, the sponsor conducted numerous various analyses of orthostatic VS for mean absolute systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse over time, and mean changes from baseline for these parameters over time, and for mean changes relative to acute dosing over time. Outliers were also assessed for increments or decrements of SBP ($\geq$ 20, $\geq$ 40 mm Hg), of DBP ($\geq$ 10, $\geq$ 20 mm Hg), and of pulse ($\geq$ 15, $\geq$ 30).

Reviewer Comment :

- Because the various analyses were so numerous and complex, I have chosen to summarize my interpretation and opinion about these results.

- I believe that it is difficult to conclude that there is a clear, unequivocal effect of lamotrigine on orthostatic VS, particularly with regard to multiplicity and numerous analyses and comparisons.

- The most consistent finding appeared to be a mild-modest change in DBP ($\geq$ 10 mm Hg), that was most commonly an increase but which was not clearly dose-related.

- Given the fact that there was not an unequivocal, clear effect of immediate-release lamotrigine on orthostatic VS, the limitations of this study design that confounded effects of dose and treatment duration, and the mild-modest effects that were suggested, mainly for DBP, it is not clear that there is a serious safety risk on orthostatic VS that must be described in the lamotrigine label.

Study Conduct

FDA Comment:
"The geographic discrepancies in outcomes seen in Study 34 are particularly troubling in light of the results of your inspection of the 2 Korean sites. As you know, we have little experience with data from many of the countries included in this study (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina), and the findings of transcription and other errors from the Korean sites appear to raise serious questions about the reliability of not only the Korean data, but data from these other countries as well , especially given the fact that neither you nor we have performed audits of many of these sites (our inspection of the Korean sites is still pending). If the data from these countries were not considered reliable, the lack of any effect seen in the U.S. centers would obviously take on even more importance."

GSK Response:
GSK has taken a comprehensive approach to addressing the Agency's comments regarding the reliability of data from all study sites. Specific responses to the issues raised by the Agency in the Approvable Letter are provided in the following sections. The order in which the Agency's comments are addressed has been re-organized to provide for greater document continuity.

Study Site Monitoring and Inspection

FDA Comment:
"In this regard, as we discussed in our telephone conversation of September 17, 2007, we ask that you submit the following information:

- *In particular, please specify and submit your Standard Operating Procedures (SOPs) for conducting not only monitoring but also inspections at study sites."*

GSK Response:
The SOPs for clinical monitoring are included in this submission (**Monitoring SOPs**: SOP-WWD-1101 v02, SOP-WWD-1102 v02, SOP-WWD-1102 v03, SOP-WWD-1103 v02, Guidance-0006 v01, DS-WWD-1103 v01, SOP-NPD-7200 v01). The SOPs guiding the routine compliance audits during the conduct of the study are also provided (**Compliance SOPs**: SOP-WWD-5009 v02, SOP-RAC-0005 v01).

Reviewer Comment :

- I believe that the SOPs are reasonable.

FDA Comments:

"• *We request that you inform us in detail about the nature and extent of all monitoring and/or inspections of Study 34 at different periods including: 1) during the conduct of the study; 2) after completion of this study, but prior to NDA 22-115 submission; and 3) after submission of NDA 22-115.*

• *Please specify which Study 34 sites were monitored or inspected at these different periods and specify the nature and extent of the monitoring including the percentage of verification of transcription of source data to CRFs for efficacy (especially data related to the primary efficacy endpoint), safety and PK data.*

• *If you or any local operating companies (including any consultants/contractors) conducted any other inspections of Study 34 sites other than the 2 Korean sites, please describe the differences between these other inspections (e.g. nature and scope) vs the nature and scope of inspections at the 2 Korean sites."*

GSK Response:
During the Conduct of the Study (Double-Blind Phase):

- Routine clinical monitoring was conducting according to the provided **Monitoring SOPs**. This monitoring consisted of:
  - Full review of source documentation for selected subjects
    - Conducted on at least 20% of subjects recruited at a site
    - All CRF entries verified against source documentation
  - Partial review of source documentation for all subjects
    - Informed consent
    - Subject eligibility relative to inclusion/exclusion criteria

- Serious adverse events and pregnancies
- All primary endpoints specified in the protocol

These activities occurred at all study sites during the conduct of the study.

- Routine compliance audits were conducted according to the provided **Compliance SOPs**. These audits consisted of:
  - Interviewing the principal investigator to ascertain the role and involvement of each site staff member in the conduct of the study.
  - Review of the investigator regulatory documents and conduct a consistency check of this documentation with the documents held centrally at GSK.
  - Review of 100% of the informed consent documents, including pharmacogenetics, for the consenting process and completeness of documentation.
  - Source documentation verification (SDV) of a sample of CRF data against subject study specific source documents (e.g. subject medical notes, equipment printouts, laboratory reports, study specific forms) for a minimum of 4 or 5% of subjects. SDV includes an examination of 4 key areas:
    1) Completeness, internal ambiguities or inconsistencies in the data recorded
    2) Eligibility of subjects
    3) Protocol compliance
    4) Quality of corresponding source documentation
  - 100% study drug handling procedures to include environmental controls, handling, storage, preparation, dispensing/return, and accountability.
  - Facility assessment (including off-site facilities) to determine if equipment is appropriate [i.e. appropriate maintenance and calibration documentation exist; storage and handling of study-related records, computers, study drugs, and biological samples is appropriate and adequately controlled (e.g. security, temperature)].

These routine compliance audits were performed at the following 6 sites during the conduct of the Double-Blind Phase:

- David Kudrow, MD, USA
- Lebron Paige, MD, USA
- Rupam Borgohain, MBBS, DM, India

- Shansher Dwivedee, MBBS, MD, DM, India
- Sang-Ahm Lee, MD, PhD, South Korea
- Nadezha Koroleva, MD, Russia

After Completion of the Double-Blind Phase, But Prior to NDA 22-115 Submission:
Routine clinical monitoring continued for the Open-Label Phase according to the provided **Monitoring SOPs**.

After Submission of NDA 22-115:
The filing of **NDA 22-115** included a locked database for **LAM100034** that represented complete and clean data to the best of GSK's knowledge at the time of the submission. However, after submission of **NDA 22-115**, discrepancies were discovered in the original submitted database. Consequently, GSK corrected those discrepancies, which resulted in an updated database for **LAM100034**. The means by which these discrepancies were discovered are described below.

- A single case report form (CRF) and database were utilized to collect and store data from both phases (double-blind and continuation phases) of the **LAM100034** study. The full CRF, both double-blind and continuation phase, remained accessible to site staff and GSK monitoring staff after the data from the double-blind phase portion of the study was submitted to the Agency. During the data clean-up process for the continuation-phase of the study, discrepancies between the source documents and

CRF pages were found in the double-blind phase data by site staff and GSK monitors. In an effort to fully disclose to GSK any potentially meaningful findings, these discrepancies were identified and sent to GSK for correction of the database. GSK Data Management also identified discrepancies in the double-blind phase data during routine clean-up of the continuation phase data. Since a single database was used to store the data from both phases of the study, these corrections to the double-blind phase data were made seamlessly along with updates and corrections to the continuation phase data. In effect, the double-blind phase database remained "live" after the submission of **NDA 22-115**.

- In anticipation for planned audits by the Agency and GSK, site staff and GSK monitors in Korea, Brazil, Russia and India elected to independently re-monitor the double-blind phase data and sent corrections to GSK for data entry.

- Based on the approvable letter for **NDA 22-115** received from the Agency on **September 21, 2007**, it was requested that GSK give careful scrutiny to the data obtained from foreign sites participating in **LAM100034**. Consequently, GSK undertook comprehensive data verification audits (DVAs) of all the subjects at all the study sites (both U.S. and non-U.S. sites). These audits were conducted by GSK Worldwide Compliance and GSK Global Clinical Operations staff and comprised a review of source documents, CRFs and data listings for:
    - Seizure Records (counts, numbers, records, dates)
    - Inclusion/Exclusion criteria

- Study Drug Dosing
- Adverse Events / Serious Adverse Events
- Vital Signs
- Concurrent Medications

The DVAs were conducted between **November 2007** and **March 2008** and led to a revised analysis of the study data in **April 2008**. As described in **Section 1.2.2** (Findings From DVAs), the rare, randomly distributed errors for the primary efficacy endpoint did not have a material impact on the original level of statistical significance or clinical interpretation of the efficacy data from **LAM100034.** The **LAM100034 Clinical Study Report** (Report RM2006/00035/01), and proposed **Prescribing Information** (m1.14.1.3) have been amended to reflect the revalidated data arising from the comprehensive DVA. Copies of these revised documents are included in this **Approvable Letter Response**. As tools to facilitate review the following documents are provided:

- An Annotated Clinical Study Report (with all changes shown).
- The Data Base Change Document contains a summary of all changes in the adverse event, seizure record and study drug dosing data sets.
- The Analyses Comparison Document contains a side-by-side comparison of key analyses from the original **Clinical Study** Report RM2006/00035/00 and the **Amended Clinical Study** Report RM2006/00035/01**.**

Reviewer Comment :

- Overall, the changes in results following the sponsor's inspections of all sites and reanalyses of efficacy and safety data were small to minimal and did not suggest a different impression or interpretation of results.

Findings from Data Verification Audits

FDA Comment:
"Please specify the detailed findings/results of all inspections of any sites after submission of NDA 22-115."

GSK Response:
Evaluation of the findings of all the database changes indicates the errors identified were:

- Rare
- 1% (234/23300 seizure records) error rate for primary efficacy data
- Random

• Not clustered by region or site

Efficacy Data:
Table 1 provides a summary of the findings for errors involving seizures data.

Table 1 LAM100034: Number of Seizure Errors - By-Country Breakdown

	No. of Subjects (ITT)	No. of Seizures Recorded	Errors							
			Seizure Record		Seizure Count		Seizure Code		Seizure Date	
U.S.[a]	84	10360	50	(0.5%)	12	(0.1%)	93	(0.9%)	4	(0.04%)
Argentina	4	203	0	na	0	na	0	na	0	na
Brazil	5	297	5	(1.7%)	2	(0.7%)	16	(5.4%)	1	(0.3%)
Chile	10	1064	1	(0.09%)	7	(0.7%)	0	na	4	(0.4%)
Germany	22	1784	15	(0.8%)	10	(0.6%)	1	(0.06%)	7	(0.4%)
India	25	3169	7	(0.2%)	12	(0.4%)	0	na	5	(0.2%)
Korea	31	2283	40	(1.8%)	6	(0.3%)	26	(1.1%)	2	(0.09%)
Russia	46	3408	52	(1.5%)	5	(0.1%)	3	(0.09%)	20	(0.6%)
Ukraine	9	732	6	(0.8%)	4	(0.5%)	0	na	0	na
Total	236	23300	176[b]		58[b]		139		43	

Note: Values in parentheses are the number of errors ÷ numer of seizures recorded.
Key:
na = not applicable.
a. Includes Puerto Rico.
b. Only changes in seizure records and seizure counts affected the primary endpoint. 176 + 58 = 234 total errors.

Table 2 shows that the rare, randomly distributed errors for the primary efficacy endpoint did not have a material impact on the original level of statistical significance or clinical interpretation of the efficacy data from study **LAM100034**.

Table 2 LAM100034: Comparison of the Primary Endpoint - Percent Change from Baseline in Weekly Seizure Frequency for All Partial Seizures

	Analysis from Original CSR[a]			Analysis from Amended CSR[b]		
	Placebo	Lamictal XR	p-value	Placebo	Lamictal XR	p-value
Escalation	N=120	N=116	0.0277	N=120	N=116	0.0271
Mean (SD)	12.0 (47.19)	20.5 (57.09)		12.7 (47.65)	21.6 (55.96)	
Median	16.3	28.0		15.6	29.8	
Min-Max					(b) (4)	
Maintenance	N=117	N=106	<0.0001	N=116	N=108	<0.0001
Mean (SD)	21.7 (59.98)	52.0 (45.60)		21.6 (56.43)	53.4 (45.57)	
Median	26.7	58.0		26.8	58.4	
Min-Max					(b) (4)	
Last 8 Weeks Maintenance	N=117	N=106	<0.0001	N=116	N=108	<0.0001
Mean (SD)	22.6 (60.73)	54.6 (46.48)		22.5 (57.22)	55.6 (46.62)	
Median	27.0	66.7		26.9	66.7	
Min-Max					(b) (4)	
Entire Treatment	N=120	N=116	0.0004	N=120	N=116	0.0001
Mean (SD)	19.7 (46.18)	34.8 (50.56)		19.3 (46.39)	35.4 (52.40)	
Median	24.2	46.1		24.5	46.6	
Min-Max					(b) (4)	

Key:
a. Original Clinical Study Report RM2006/00035/00 (submitted November 22, 2006 in NDA 22-115).
b. Amended Clincial Study Report RM2006/00035/01.

Safety Data:
With regard to the safety data for study **LAM100034**, a total of 74 adverse events (AEs) were added to the database and 40 AEs were deleted from the database. Reasons for these additions and deletions included changes to the AE start dates, changes to the AE end dates, and changes made for proper coding of the AE terms. Additionally, there were changes in serious adverse events (SAEs) for two subjects:

- In the first subject, there were changes in two SAEs. The SAE of dehydration was deleted by the site and confirmed as appropriate, and the SAE of diabetic ketoacidosis did not occur during the double-blind phase because of a date change on the dosing record.

- In the second subject, one new SAE (gastritis erosive) was reported after the NDA database was locked and has subsequently been added to the amended database.

The interpretation of safety data included in the original study report and NDA remains unchanged.

Reviewer Comment :

- I concur with the sponsor's conclusion. Overall, the revisions to summary data analyses for efficacy and safety were quite small and of no clear substance that would alter any previous impression or interpretation of the data.

Additional Ad-Hoc Analyses Requested by the Agency During NDA Review

A number of additional safety analyses were requested by the Agency during the review of **NDA 22-115**. These analyses have been updated using the amended database. In the Guide to FDA Requested Safety Analyses, links to the individual tables can be found.

Reviewer Comment :

- There was no substantial difference in the results of these reanalyses.

Integrity of Data from Foreign Sites

FDA Comment:
"Please address our concerns, raised by the results of the Korean inspections, about the integrity of the data at the foreign sites that have not been audited/inspected."

GSK Response:
The integrity of the **LAM100034** study data has been carefully evaluated and re-established through the comprehensive DVAs conducted on all study subjects at all clinical sites.

FDA Comment:
"Please submit the results of your planned reanalyses after corrections of the data from the 2 Korean sites as well as the detailed findings of the audit of these two sites."

GSK Response:
The details of the Korean audits have previously been submitted to the Agency (submission date: **September 20, 2007**). Upon reaching the decision to conduct comprehensive DVAs at all study sites, the initial plan for a reanalysis including corrected data from the Korean study sites was subsumed by the comprehensive reanalysis of revalidated data from the DVAs. As stated above, NDA documents [e.g., **Clinical Study Report** RM2006/00035/01 and proposed **Prescribing Information** (m1.14.1.3)] affected by the reanalysis have been revised and are included to this submission.

Reviewer Comment :

- I believe that the results of the inspections of all sites did not suggest fraud nor unusually "sloppy" practices for collection of clinical data. The sponsor provided an informative presentation of findings of inspections for all sites.

- The DSI inspections of the Russian sites suggested that quality of data collection was reasonably good and did not suggest any significant concerns.

Safety Update

The approvable letter also made the following requests (shown in italics) for updated safety information.

"When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.
1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
• Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
• Present tabulations of the new safety data combined with the original NDA data ***showing these different datasets in the same table****.*
• Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
• For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies and by ***showing these different datasets in the same table****. Describe any new trends or patterns identified.*
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted."

Safety Update

Sponsor's Synopsis of Safety Update

Overview

The sponsor noted that this Final Safety Update report updates the safety profile for lamotrigine extended release (XR) tablets by summarizing safety information available since the cut-off date for safety information in NDA 22-115 (28 June 2006) through the cut-off date of 31 January 2008 for the update. This report includes safety information from one completed (LAM105379) and one ongoing (LEP111102) clinical pharmacology study and from three ongoing (LAM100034, LAM100036, LAM30055) clinical studies. Data from LAM105379 and from LAM30055 were being presented for the first time and were presented individually. Data from LAM100034 and LAM100036 were presented as follows:
• Combined LAM100034/LAM100036 – as in the original NDA, as interval safety data from the NDA cut-off date (28 June 2006) to Final Safety Update cut-off date (31 January 2008) and as original NDA data updated with the interval safety data.

Safety Information from Completed Studies

Clinical Pharmacology Studies
LAM105379
LAM105379 was an open-label, randomized bioequivalence and food effect study of 300 mg/day of lamotrigine extended-release in healthy volunteers.

One hundred and eighty subjects were exposed to lamotrigine XR during this study; 120 subjects received the 300mg single dose and 60 subjects received a reference dose comprised of a 100mg plus a 200mg XR tablet. All doses of lamotrigine XR were well tolerated in the fasted and fed states and there were no clinically significant safety findings. There was one serious adverse event (SAE) of multiple injuries which was unrelated to study drug.

Clinical Studies
No clinical studies completed during this reporting interval.

Safety Information from Studies in Progress
Clinical Pharmacology Studies
LEP111102 is an open-label, randomized bioequivalence and food effect study of a 250 mg/day lamotrigine extended-release tablet in healthy volunteers. As of the data cut-off date, there were no deaths, SAEs or discontinuations due to adverse events (AE).

Clinical Studies
LAM100034: This is a placebo-controlled, double-blind study with an open-label continuation phase. This study evaluated the effectiveness of lamotrigine XR tablets for the treatment of partial seizures. The Double-Blind Treatment data were submitted in NDA 22-115. The open-label Continuation Phase of LAM100034 is ongoing at the time of this Final Safety Update.

LAM100036: This is a placebo-controlled, double-blind study with an open-label continuation phase. This study evaluated the effectiveness of lamotrigine XR tablets for the treatment of primary generalized tonic-clonic seizures. The open-label Continuation Phase of LAM100036 is ongoing at the time of this Final Safety Update.

LAM30055: This is a double-blind, randomized conversion to monotherapy comparison of two doses (250 mg/d and 300 mg/d) of lamotrigine XR for the treatment of partial seizures.

As these studies are ongoing, available data are limited to deaths, SAEs, and discontinuations due to adverse events (AEs) for the reporting period 29 June 2006 to 31 January 2008. In addition, information regarding common AEs are included in this update only for the combined, unblinded data from LAM100034 and LAM100036.

There were a total of 114 new subject exposures to lamotrigine XR in studies LAM100034 and LAM100036 during this reporting period. While LAM30055 is a randomized, blinded study, all subjects receive lamotrigine XR and approximately 136 subjects were exposed during the reporting period.

The initial NDA 22-115 submission included an integrated analysis of SAEs from the Double-Blind and Continuation Phases of study LAM100034 and the Continuation Phase of Study LAM100036 (unblinded subjects). At that time, the overall incidence of SAEs for these unblinded subjects was 4% (13/311 subjects). At the data cut-off date for this Final Safety Update, the cumulative incidence of SAEs for LAM100034 and LAM100036 was 7% (31/425 subjects).

There were 2 new fatal SAEs during this reporting period.

Across the three studies, there were 41 treatment-emergent SAEs reported for 28 subjects during this reporting period. Twelve of the subjects experiencing SAEs were in study LAM100034, and 7 subjects were in study LAM100036. Eleven SAEs in 7 subjects were considered to be related to study drug. Only dizziness was reported as serious in more than 1 subject. Three subjects withdrew from the studies due to a SAE. In LAM30055, 9 subjects reported 12 SAEs. No SAE occurred in more than 1 subject. Four subjects discontinued due to SAE.

A total of 8 subjects withdrew from LAM100034/LAM100036 due to an AE during the reporting period: 5 subjects from LAM100034 and 3 subjects from LAM100036. Five AEs leading to withdrawal of 4 subjects were SAEs (ataxia, dysarthria, acute cardiac failure, drug toxicity and hydrocephalus). In LAM30055, 19 subjects withdrew due to AE. Rash (6 subjects) was the most frequently-cited reason.

Four pregnancies were reported during the reporting interval. Three occurred in study LAM100036 and 1 in LAM30055. Outcome of 3 pregnancies is known (1 normal birth, 1 spontaneous miscarriage at approximately 12 weeks gestational age, and 1 elective termination).

The most common treatment-emergent AEs in subjects from the integrated data across studies LAM100034 and LAM100036 are summarized in Table 12 .

Table 12 Most Common AEs (Greater Than or Equal to 5% in Any Reporting Period) (Unblinded Safety Population: Studies LAM100034 and LAM100036 - Combined)

Adverse Event	Number (%) of Subjects		
	Initial NDA	New Information Obtained During reporting Period	Cumulative Total
	N=311	N=425	N=425
Any Event	158 (51)	184 (43)	301 (71)
Headache	41 (13)	52 (12)	93 (22)
Dizziness	39 (13)	29 (7)	75 (18)
Nausea	21 (7)	10 (2)	36 (8)
Vomiting	14 (5)	15 (4)	34 (8)
Tremor	12 (4)	14 (3)	27 (6)
Somnolence	13 (4)	6 (1)	21 (5)
Diplopia	8 (3)	10 (2)	27 (6)
Nasopharyngitis	7 (2)	12 (3)	23 (5)

Data Source: Appendix 2, NDA 22-115,Table 5.24; Section 10, Table 5.6, Table 5.7, Table 5.13 and Table 5.14

Data from the reporting period are in line with AE frequency data reported in the NDA. The most frequently-reported AEs are headache and dizziness. Internal auditing of study data from LAM100034 Double-Blind phase resulted in changes in occurrence of AEs from that reported in the NDA. In many cases, the changes were due to additional events that had occurred during the NDA reporting period, but had not been captured in the case report forms from which the NDA submission was compiled.

The Cumulative Total column shows an increase in the event frequency of some AEs, but does not indicate a substantial alteration in the relative frequency of AEs. An increase in frequency would be expected as the Cumulative Total represents the longer period of exposure subjects experienced through completion of the open-label Continuation Phase of the studies.

Deaths

Deaths in the Unblinded Safety Population

Data listings of subject deaths are presented in Table 13.

Table 13 Listing of Subject Deaths (Unblinded Safety Population: Studies LAM100034 and LAM100036 – Combined)

Blinded/ Unblinded	Study	Subj. No	Age	Sex	Race	AE	Related to Study Drug	In NDA
Unblinded	LAM100034	1546	38	F	Asian	Aspiration during GTC seizure	No	Yes
Unblinded	LAM100034	2094	35	F	White	Acute cardiac failure	Yes	No
Unblinded	LAM100034	2152	22	F	White	Acute poisoning by LTG (Drug toxicity)	Yes	Yes[a]
Unblinded	LAM100036	1578	15	F	Asian	Hydrocephalus	No	No

Data Source: Appendix 2, NDA 22-115, Table 5.58; Section 10, Table 5.10, Table 5.17
a. Subject 2152 died after NDA data cut-off.

Four deaths were reported among subjects who were randomized to, and received, lamotrigine XR. Two of these deaths (subjects 2094 and 1578) occurred during the reporting interval. Subject 2094 had received lamotrigine XR for 14 months in LAM100034. She died suddenly of acute heart failure. An autopsy revealed ischemic heart disease. Subject 1578 received treatment with lamotrigine XR for 6 months when she presented with hemiparesis and left-sided hydrocephalus. A VP shunt was placed and subject initially showed signs of response, but died 2 days after the surgery.

Subject 2152 died after the cut-off date for the initial NDA. However, the sponsor became aware of the death during preparation of the NDA and included it in NDA 22-115.

In addition, subject 62 in LAM100034, who was randomized to lamotrigine XR, died prior to receiving study medication. The cause of death was complex partial seizure and was not considered to be related to lamotrigine XR since it occurred prior to the receipt of any study drug.

Deaths in the Blinded Safety Population

There were no deaths reported in LAM30055 at the time of data cut-off.

Other Serious Adverse Events

SAEs in the Unblinded Safety Population

SAEs reported by subjects in the unblinded portions of LAM100034 and LAM100036 are summarized in Table 14.

Table 14 Serious Adverse Events (Unblinded Safety Population: Studies LAM100034 and LAM100036- Combined)

Serious Adverse Event	Number (%) of Subjects		
	Initial NDA	New Information Obtained During reporting Period	Cumulative Total
	N=311	N=425	N=425
Any Event	13 (4)	19 (4)	31 (7)
Dizziness	1 (<1)	1 (<1)	2 (<1)
Nystagmus	2 (<1)		2 (<1)
Vomiting	1 (<1)	1 (<1)	2 (<1)
Ataxia		1 (<1)	2 (<1)
Abasia		1 (<1)	1 (<1)
Abdominal pain	1 (<1)		1 (<1)
Abortion spontaneous		1 (<1)	1 (<1)
Altered state of consciousness		1 (<1)	1 (<1)
Ankle fracture	1 (<1)		1 (<1)
Aspiration	1 (<1)		1 (<1)
Astrocytoma		1 (<1)	1 (<1)
Bile duct cancer		1 (<1)	1 (<1)
Brain contusion		1 (<1)	1 (<1)
Cardiac arrest			1 (<1)
Cardiac failure acute		1 (<1)	1 (<1)
Cervical spinal stenosis			1 (<1)
Cholecystitis acute		1 (<1)	1 (<1)
Cholelithiasis		1 (<1)	1 (<1)
Complex partial seizure	1 (<1)		1 (<1)
Confusional state		1 (<1)	1 (<1)
Contusion		1 (<1)	1 (<1)
Dehydration	1 (<1)		
Diabetic ketoacidosis	1 (<1)		1 (<1)
Drug toxicity		1 (<1)	1 (<1)
Dysarthria		1 (<1)	1 (<1)
Food poisoning		1 (<1)	1 (<1)
Gastritis	1 (<1)		1 (<1)
Gastroenteritis viral	1 (<1)		1 (<1)
Grand mal convulsion	1 (<1)		1 (<1)
Headache	1 (<1)		1 (<1)
Hemiparesis		1 (<1)	1 (<1)
Infection		1 (<1)	1 (<1)
Intentional overdose	1 (<1)		1 (<1)
Intervertebral disc protrusion		1 (<1)	1 (<1)
Malignant hypertension	1 (<1)		1 (<1)
Multiple fractures		1 (<1)	1 (<1)
Myocardial infarction	1 (<1)		1 (<1)
Nausea	1 (<1)		1 (<1)
Pancreatitis	1 (<1)		1 (<1)
Partial seizures	1 (<1)		1 (<1)
Partial seizure with secondary generalization			1 (<1)
Pelvic fracture		1 (<1)	1 (<1)
Pneumonia viral	1 (<1)		1 (<1)
Pyelonephritis acute	1 (<1)		1 (<1)
Skin laceration		1 (<1)	1 (<1)
Skull fracture		1 (<1)	1 (<1)
Status epilepticus	1 (<1)		1 (<1)
Suicide attempt		1 (<1)	1 (<1)
Syncope vasovagal		1 (<1)	1 (<1)
Tibia fracture	1 (<1)		1 (<1)
Traumatic brain injury		1 (<1)	1 (<1)
Uterine leiomyoma		1 (<1)	1 (<1)
Sudden death	1 (<1)		

Data Source: Appendix 2, NDA 22-115, Table 5.50; Section 10, Table 5.8, Table 5.9, Table 5.15 and Table 5.16

Discrepancies in number of events among the reporting groups are due to time of event or coding change that occurred in the ongoing studies as a result of information obtained after filing of the NDA. Descriptions of discrepancies are provided in APPENDIX 3.

Nineteen (4%) new subjects experienced 29 SAEs during the reporting interval. Therefore, a total of 31 (7%) subjects had experienced 56 SAEs in the unblended population by the time of data cut-off. Only 4 SAEs (dizziness, nystagmus, vomiting and ataxia) were reported by more than 1 subject (each reported by 2 subjects). Seven subjects reported 11 SAEs considered by the investigator to be related to lamotrigine and these are listed in Table 15.

Table 15 Serious Adverse Events Related to Lamotrigine (Unblinded Safety Population: Studies LAM100034 and LAM100036 – Combined)

Study	Subj. No.	SAE	Severity
LAM100034			
	218	Ataxia	Mild
		Vomiting	Moderate
	1554	Abasia	Mild
		Dizziness	Mild
	1534	Pancreatitis	Moderate
	1840	Dizziness	Severe
		Headache	Severe
		Nystagmus	Severe
	2094	Acute heart failure	Fatal
	2152	Acute poisoning, lamotrigine	Fatal
LAM100036			
	1641	Spontaneous abortion	Moderate

Data Source: Section 10, Table 5.16

Two of these had fatal outcomes; acute heart failure and acute poisoning with lamotrigine. In the case of acute heart failure, an autopsy was performed and a diagnosis of ischemic heart failure was also noted which may have contributed to the death. In the case of acute lamotrigine poisoning, although the cause of death is ascribed to acute lamotrigine poisoning in this event, there is no information on lamotrigine concentrations from the autopsy to indicate that the patient had excessive lamotrigine levels. An intentional lamotrigine overdose is suggested as the underlying cause but there is also no information from the available medical history to indicate an overdose. Based on the available information it is not possible to exclude a causal relationship with lamotrigine.

SAEs in the Blinded Safety Population

In LAM30055, 9 subjects reported 12 SAEs. No SAE occurred in more than 1 subject. Two (grand mal seizure and drug eruption) were considered by the investigator to be related to study drug. Six events were unresolved at the time of data cut-off. Four subjects discontinued study drug due to SAE.

Other Significant Adverse Events

Adverse events leading to permanent treatment discontinuation – Unblinded Safety Population

AEs leading to discontinuation from the unblinded portions of LAM100034 and LAM100036 are summarized in Table 16

Table 16 Adverse Events Leading to Premature Discontinuation (Unblinded Safety Population: Studies LAM100034 and LAM100036)

Treatment-Ending Adverse Event	Number (%) of Subjects		
	Initial NDA	New Information Obtained During reporting Period	Cumulative Total
	N=311	N=425	N=425
Any Event	16 (5)	8 (2)	27 (6)
Dizziness	5 (2)	1 (<1)	7 (2)
All rash[a]	2 (<1)	1 (<1)	5 (1)
Nystagmus	2 (<1)		3 (<1)
Asthenia	2 (<1)		2 (<1)
Ataxia	2 (<1)	1 (<1)	2 (<1)
Headache	2 (<1)		2 (<1)
Nausea	3 (<1)		2 (<1)
Vertigo	2 (<1)	1 (<1)	2 (<1)
Dysarthria		1 (<1)	1 (<1)
Abdominal pain		1 (<1)	1 (<1)
Anxiety	1 (<1)		1 (<1)
Aspiration	1 (<1)		1 (<1)
Cardiac failure acute		1 (<1)	1 (<1)
Depression	1 (<1)		1 (<1)
Diplopia	1 (<1)		1 (<1)
Drug toxicity		1 (<1)	1 (<1)
Gait disturbance	1 (<1)		1 (<1)
Grand mal convulsion	1 (<1)		1 (<1)
Hot flush	1 (<1)		1 (<1)
Hydrocephalus		1(<1)	1 (<1)
Malaise	1 (<1)		1 (<1)
Oscillopsia			1 (<1)
Pancreatitis	1 (<1)		1 (<1)
Psychomotor retardation	1 (<1)		1 (<1)
Simple partial seizure			1 (<1)
Somnolence		1 (<1)	2 (<1)
Status epilepticus	1 (<1)		1 (<1)
Stomach discomfort	1 (<1)		1 (<1)
Tremor	1 (<1)		1 (<1)
Vomiting			1 (<1)
Intention tremor	1 (<1)		
Sudden death	1 (<1)		

Data Source: Appendix 2, NDA 22-115, Table 5.62; Section 10, Table 5.11, Table 5.12, Table 5.18 and Table 5.19
a. All Rash includes Rash and Rash generalized

Discrepancies in number of events among the reporting groups are due to time of event, categorization or coding changes that occurred in the ongoing studies as a result of information obtained after filing of the NDA.

During the reporting interval, 8 subjects experienced 10 AEs leading to withdrawal. Therefore, a total of 27 (6%) subjects had experienced 51 AEs leading to discontinuation at the time of data cut-off. The most frequent AEs leading to discontinuation were dizziness (N=7), and rash (N=5). All others occurred at <1% frequency. In LAM30055, 19 subjects discontinued treatment because of AEs. Most were of moderate intensity. Rash (6 subjects) was the most frequently-

cited reason. Two of the rashes were of mild intensity; none was severe. Four of the AEs leading to discontinuation were considered to be serious by the investigator.

Post-Marketing Data
The safety of lamotrigine is reviewed on an ongoing basis by the Global Clinical Safety and Pharmacovigilance department (GCSP) at GlaxoSmithKline (GSK). Adverse event reports are received from all sources including clinical trials, spontaneous reports, regulatory authorities, published literature and from post-marketing surveillance studies.

These data are analysed in a cumulative setting to identify any potential new safety signals. Any adverse drug reactions identified that are considered causally related to lamotrigine are then incorporated into the GSK lamotrigine Global Data Sheet (GDS) and local prescribing information. Any updates to the GDS are also documented in the lamotrigine Periodic Safety Update Reports (PSURs).

The last integrated safety summary for lamotrigine provided to the FDA included safety data up to 31 October 1997. Hence for this safety summary, the GSK clinical safety database was searched with a data-lock point from 01 November 1997 to 30 September 2007, to identify all post-marketing reports (spontaneous and post-marketing surveillance) where lamotrigine was reported as a suspect drug.

The events reviewed in Module 5.3.6 are of special interest and have been the subject of many reviews up to this date. Much of this previous work has led to changes in the product labeling in order to minimize any known risks associated with lamotrigine treatment. Consequently the product labeling for LAMICTAL™ provides extensive information and guidance in relation to particular events, especially serious skin reactions, hypersensitivity reactions and multi-organ failure. Other events are the subject of ongoing evaluations to further define the benefit risk profile in these populations, for example the suicide analysis of clinical trial data and pregnancy registries. GSK believes that this review confirms the known safety profile of lamotrigine and the current product labeling accurately reflects this profile.

Sponsor Conclusions

This Final Safety Update report updates the safety profile for lamotrigine XR tablets by summarizing information available since the cut-off date for safety information in NDA 22-115 (28 June 2006) through the cut-off date of 31 January 2008. This report includes safety information from one completed clinical pharmacology study and three ongoing clinical studies.

During this update period, there were a total of 430 new subject exposures to lamotrigine XR (180 in clinical pharmacology study LAM105379, 114 in ongoing unblinded portions of clinical studies LAM100034 and LAM100036 and 136 new subject exposures to blinded study drug in the Double-Blind Treatment Phase of LAM30055). A total of 1004 subjects have now been exposed to lamotrigine XR.

Lamotrigine XR was well tolerated in the clinical pharmacology study. The most common AEs were headache and fatigue and were, overall, consistent with the constellation of AEs in other clinical pharmacology studies with lamotrigine previously provided in the initial NDA 22-115 submission. There was one new SAE: accident requiring hospitalization and withdrawal from the study. The event was considered not related to study drug. There were no other withdrawals due to AE and no pregnancies were reported during the study.

In the three ongoing clinical studies (unblinded data from LAM100034 and LAM100036 combined and blinded LAM300055), 3 of the 5 total deaths occurred during this reporting interval, but 1 was reported in NDA 22-115. One additional death occurred prior to start of dosing with study drug. In combined, unblinded data from LAM100034/LAM100036, there were 29 additional treatment-emergent SAEs reported for 19 subjects. Only 4 SAEs (ataxia, dizziness, nystagmus and vomiting) were reported by more than 1 subject (each reported by 2 subjects).

During the reporting period, a total of 8 subjects (2%) withdrew due to an AE. Blinded narratives from LAM30055 show 9 subjects reported 12 SAEs and 19 subjects withdrew due to AE. Four subjects became pregnant during the reporting period.

The cumulative incidence of SAEs in LAM100034 and LAM100036 combined increased from 4% to 7% during the reporting period. An increase in the cumulative incidence of SAEs is not unexpected given the length of the Continuation Phases of both LAM100034 and LAM100036 (52 weeks for subjects who were in the Double-Blind Treatment Phase and 26 weeks for Baseline Failures).

Post-marketing reports (spontaneous reports and published literature) of deaths, serious adverse events, serious skin rash, and multi-organ failure for the reporting period are consistent with those reported previously in the initial NDA 22-115 submission. The additional clinical pharmacology data and data from clinical trials continue to support the conclusions reached in the initial NDA 22-115 submission. These new data have no impact on the interpretation of the safety data submitted with the application. Lamotrigine XR continues to have an acceptable safety and tolerability profile as described in NDA 22-115.

Sponsor's Review of Post-Marketing Experience

Sponsor's Introduction

The safety of lamotrigine is reviewed on an ongoing basis by the Global Clinical Safety and Pharmacovigilance department (GCSP) at GlaxoSmithKline (GSK). Adverse event reports are received from all sources including clinical trials, spontaneous reports, regulatory authorities, published literature and from post-marketing surveillance studies.

These data are analysed in a cumulative setting to identify any potential new safety signals. Any adverse drug reactions identified that are considered causally related to lamotrigine are then incorporated into the GSK lamotrigine Global Data Sheet (GDS; which encompasses the core

safety information) and local prescribing information. Safety related updates to the GDS are also documented in the lamotrigine Periodic Safety Update Reports (PSURs).

Lamotrigine (LAMICTAL®) immediate release (IR) tablets was first approved on 05 November 1990 in Ireland for use as add-on therapy in adult patients with partial seizures and generalized tonic-clonic seizures and is now available in over 100 countries. In the USA, LAMICTAL was initially approved in December 1994 and launched in February 1995 for adjunctive use in adults with partial seizures. Subsequently, lamotrigine was also approved for the prevention of mood episodes in patients with bipolar disorder, and is now available in over 50 countries for this indication.

Exposure to lamotrigine is extensive following over 17 years of market experience and the adverse event profile is well characterized. The cumulative world-wide exposure to lamotrigine (all indications) from launch up to 30 November 2007 is approximately 8.6 million patient-years.

This estimate is based on the available sales volume data, from the Intercontinental Medical Statistics database, MIDAS.

Sponsor's Overview of post-marketing serious adverse event reports

The last integrated safety summary for lamotrigine provided to the FDA included safety data up to 31 October 1997. Hence for this safety summary, the GSK clinical safety database was searched with a data-lock point from 01 November 1997 to 31 January 2008, to identify all post-marketing reports (spontaneous and post-marketing surveillance) where lamotrigine was reported as a suspect drug. These reports were then further limited to those that met the regulatory seriousness criteria and where the patients were aged over 12 years or their age was unknown. NB. Some pregnancy reports describing fetal/neonatal outcomes will also be included as a result of GSK's pregnancy coding convention.

The above described search retrieved a total of 6847 reports. These post-marketing reports were received either from healthcare professionals (67%), non-healthcare professional (i.e. consumers, lawyers, other manufacturers) (15%), directly from regulatory authorities (13%) or from the published medical literature (5%). The majority of reports were received from the USA (46%), UK (11%), Germany (9.5%) and France (8%). No other one country contributed to more than 3% of the reports. The indication for the use of lamotrigine was epilepsy in 44% of the reports, mood disorders in 30%, unknown indication in 23%, and other off label use (i.e. pain, schizophrenia) accounted for 3% of the reports. There were 5165 reports where the exact age of the patients was specified (minimum 13 years, maximum 97 years, and median 36 years). A further 486 patients specified an approximate age group and the remaining 1196 patients were of unknown age. The sex of the patients was specified in 6384 reports, of which 4478 were female and 1906 were male. Of these 6847 serious reports, 394 reported a fatal outcome and 6453 did not.

Sponsor's Overall Conclusion

The safety of lamotrigine is reviewed on an ongoing basis by the Global Clinical Safety and Pharmacovigilance department at GSK. The events reviewed in this document are of special interest and have been the subject of many reviews up to this date. Much of this previous work has lead to changes in the product labeling in order to minimize any known risks associated with lamotrigine treatment. Consequently the product labeling for LAMICTAL provides extensive information and guidance in relation to particular events, especially serious skin reactions, hypersensitivity reactions, multi-organ failure and suicidal behavior/ideation. The use of the pregnancy registries is the subject of ongoing evaluations to further define the benefit risk profile in these populations. GSK believes that this review confirms the known safety profile of lamotrigine and the current product labeling accurately reflects this profile.

Reviewer Comment :

- I agree with the sponsor that the Safety Update and review of post-marketing experience did not suggest a change in the safety profile for XR lamotrigine nor that recognized for the immediate-release formulation of lamotrigine.

5. PHARMCOKINETIC, EFFICACY, AND SAFETY DATA IN PEDIATRIC PATIENTS (13-16 YEARS)

Pharmacokinetic (PK) Data

The following table summarizes the number of adolescent patients in an older range of pediatric patients (≤ 16 years) and lowest range of adults (17-18 years). Although there were 6 XR lamotrigine patients randomized, three of these patients did not have any PK samples (e.g. one patient discontinued from the study after a few days of treatment and another did not have any PK samples). Only 4 pediatric patients (13 or 14 years old) had PK samples.

Age	Number of Subjects on Lamictal XR	Number of Subjects on Placebo	Number of Subjects with Lamictal-PK	Subject IDs (# of PK samples)
13	3	0	1	033 (4)
14	3	1	3	022 (5) 1537 (4) 2127 (6)
15	0	3	0	
16	0	1	0	
17	5	3	3 +2 (with 1 sample)	1536 (4) 2121 (6) 2165 (5) 1508 (1) 2136 (1)
18	3	2	3	1541 (4) 2051 (4) 2123 (6)

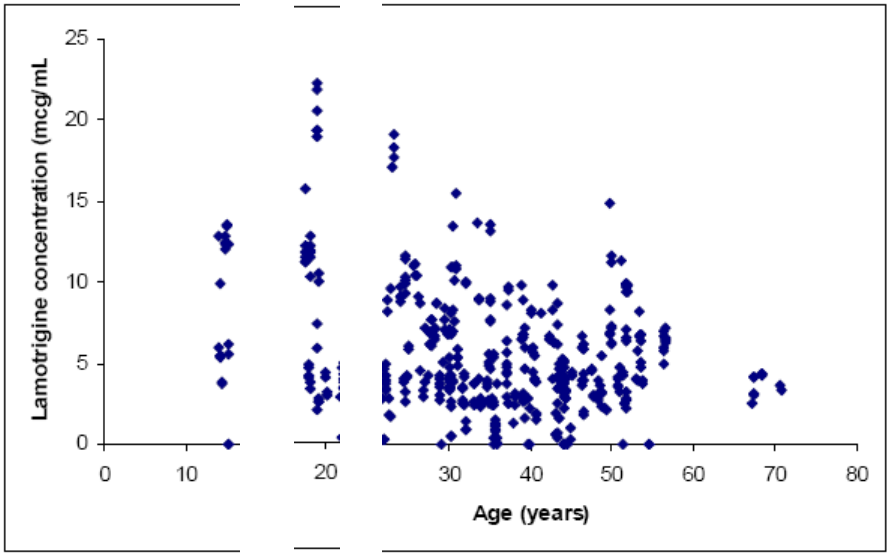
Of potential interest, the sponsor's population PK report noted that Subject 22, who was 14 years old, had very high predicted lamotrigine concentrations according to modeling despite the fact that his actual observed concentrations appeared to be within the "normal range."

Lamotrigine concentration data for subject 22 are provided below.

ID	CENT	DOSE	TRT	NDAY	DATE	TIME	TIME AFTER DOSE (h)	LTG CONC (ug/mL)
(b) (4)								

Subject 22 was receiving 200 mg XR lamotrigine at the time of all PK samples and was also receiving valproate and levetiracetam as concomitant AEDs during the whole treatment period. The dose regimen of lamotrigine for Subject 22 was similar to all other subjects. However, this subject had the lowest weight (24 kg or 53 lbs) compared to equivalent subjects (U.S., valproic acid co-medication) (46 to 122 kg). Lamotrigine concentrations versus population and individual predictions were investigated to show the plots of residuals versus population predictions and time after dose, the plot of weighted residuals versus population predictions and time after dose. Because decreases in the inter-individual variability on PK clearance (CL), and the residual error variance terms was seen when subject 22 was excluded, subject 22 was excluded from any subsequent analysis. The original final model was re-fitted with this subject excluded.

The following figure shows the lamotrigine concentrations in all patients during the maintenance period at PK steady state. I have separated this figure into three parts to facilitate focus on results for the only pediatric patients (13-14 years old) who had PK samples, for young adults 17-21 years), and for older adults (≥ 22 years old).



Reviewer Comment :

- According to my "eyeballing" guestimates of mean levels, I suggest that the mean lamotrigine concentration was ~ 8 for patients 13-14 years old, ~ 12 for very young adult patients 17-21 years old, and ~ 5 for patients ≥ 22 years old. My "eyeball" guestimate for all adults (≥ 17 years old) would be ~ 6. Thus, I question whether lamotrigine concentrations in pediatric patients may be higher than those of all adults. I also wonder if it is possible (considering that levels in older adolescent and young adulthood seem somewhat higher) that perhaps higher levels might be observed in 15 -16 year old patients who were not treated with lamotrigine and for whom there are no PK levels in these patients. My speculation is based upon the observation that relatively higher levels appeared to occur in young adults (17-21 years old) compared to older adults (≥ 22 years old).

- I recognize that there is no clear scientific reason to expect that pharmokinetics and lamotrigine levels in older pediatric patients (13-16 years) are different from those of adults would be different. However, my typical practice is an empirical approach is to draw conclusions from sufficient, observed data and not to rely on assumptions. **Thus, I think that it is best to have reasonably adequate data to draw conclusions. I am unable to conclude that the available data are sufficient or adequate to draw conclusions that the PK in pediatric adolescents (13-16 years) is similar to the PK of adults (> 17 years).**

- I recognize that my concerns, questions, and reservations about whether PK levels in older pediatric patients (13-16 years old) may be different from those of adults (≥ 17 years) are not based upon clear, robust or sufficient data (e.g., data were derived from only 4 pediatric patients and all these patients were 13-14 years old) to draw an appropriate conclusion. In summary, I think that the existing pediatric PK data are insufficient/inadequate to draw a reliable conclusion about whether PK in pediatric patients 13-16 years old is similar to PK in adults (≥ 17 years old).

Pediatric Efficacy Data

Table 7.R
Summary of Percent Change from Baseline in Weekly Seizure Frequency
For Patients 16 Years of Age or Younger

Seizure Type	Treatment Period	Treatment Group	n	Mean	SD	Median	Min.	Max.
All Partial Seizures	Baseline [1]	Placebo	5	9.9	10.69	4.8		(b) (4)
		Lamictal XR	5	5.4	6.30	2.6		
	Escalation	Placebo	5	17.5	51.23	33.3		
		Lamictal XR	5	13.9	107.43	89.1		
	Maintenance	Placebo	5	5.3	36.72	6.7		
		Lamictal XR	5	64.9	66.16	93.9		
	Last 8 wks Maintenance	Placebo	5	6.1	30.88	12.0		
		Lamictal XR	5	66.9	61.15	100.0		
	Entire Treatment	Placebo	5	12.8	42.89	29.8		
		Lamictal XR	5	16.8	106.09	85.9		

Reviewer Comment :

- The efficacy data (see preceding Table 7.R) in 10 pediatric (13-16 years) patients (N= 5 in each group) suggested possible efficacy of XR lamotrigine (86 % median reduction in seizure rate from baseline) vs placebo (30 % reduction) for the primary efficacy endpoint for the entire treatment period, and the treatment difference/effect (XR lamotrigine % - placebo %) was even greater. However, these results are based upon a very small number of patients and the mean change from baseline show no clear difference (XR 17 % vs placebo 13 %). This striking difference in summary descriptive results for the mean % change from baseline (vs the median % change from baseline) indicates that these data are not normally distributed.

- Furthermore, the baseline seizure frequency was almost twice as great for the placebo group as for the XR lamotrigine group, perhaps favoring the XR lamotrigine group because the seizure frequency was considerably lower. For placebo patients, the mean seizure rate was 9.9 and the median was 4.8. For XR lamotrigine patients, the mean seizure rate was 5.4 and the median was 2.6.

- At best, one could surmise that these results are consistent with a possible therapeutic benefit of XR lamotrigine in pediatric patients, but they are certainly not seriously indicative of such a benefit.

Listing 7.S
Listing of Percent Change from Baseline in Weekly Seizure Frequency for All Partial Seizures
For Patients 16 Years of Age or Younger

Treatment	Center	Subj.	Age	Duration of Treatment (weeks)	Baseline Weekly Seizure Frequency	Treatment Period	Percent Change from Baseline in Weekly Seizure Frequency
Placebo	007572	23	16	19	27.0	Escalation	(b) (4)
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	011396	1510	14	19	13.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	012925	1535	15	19	1.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021281	2125	15	19	4.8	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021491	1809	15	11	2.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
Lamictal	007572	22	14	19	16.3	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
Lamictal	008565	33	13	19	5.6	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	012925	1534	13	7	1.3	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
		1537	14	19	1.4	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021281	2127	14	19	2.6	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	

Reviewer Comment :

- Listing 7.S shows the % change of seizure rate from baseline for the escalation period, maintenance period, and the whole study period. This listing suggested that three pediatric placebo-treated patients (ID #s 1535, 2125, 1909) appeared to have reasonable treatment "responses" over the entire treatment period consisting of 30, 45, and 41 %, respectively, reductions in seizure rate from baseline. This efficacy outcome was the primary efficacy endpoint. Two placebo patients did not appear to have "responses" (8 % decrease, and 60 % increase in seizure rate). This listing also showed that 3 XR

lamotrigine patients (ID#s 33, 1537, 2127) appeared to have "responses" over the entire treatment period consisting of (b) (4) %, respectively, reductions in seizure rate from baseline. These "responses" were greater in magnitude that those of the placebo patients. Two XR lamotrigine patients did not appear to have "responses" (55 % and 135 % increase in seizure rate).

Of note, patient # 1534 appeared to have a (b) (4) % reduction in seizure rate in the maintenance period. However, the representation of this result is misleading because this patient discontinued from the study after only 1 day in the maintenance period and the sponsor calculated that because the patient did not have any seizures during that short time in the maintenance period, that there was a complete (b) (4) % reduction in seizure rate over the entire maintenance period that should have consisted of 12 weeks.

Table 7.W
Summary of Weekly Seizure Frequency
For Patients 16 Years of Age or Younger

Seizure Type	Treatment Period	Treatment Group	n	Mean	SD	Median	Min.	Max.
All Partial Seizures	Baseline	Placebo	5	9.85	10.691	4.75		(b) (4)
		Lamictal XR	5	5.42	6.302	2.63		
	Escalation	Placebo	5	12.31	19.107	2.43		
		Lamictal XR	5	5.97	11.177	0.57		
	Maintenance	Placebo	5	12.15	17.166	2.77		
		Lamictal XR	5	5.17	11.001	0.08		
	Last 8 wks Maintenance	Placebo	5	11.47	15.968	2.88		
		Lamictal XR	5	4.85	10.094	0.00		
	Entire Treatment	Placebo	5	12.14	17.930	2.64		
		Lamictal XR	5	5.83	10.896	0.79		

Reviewer Comment :

- Efficacy data in 10 pediatric (13-16 years) patients (N= 5 in each group) are shown for absolute seizure rates in the preceding Table 7.W. If one looks at the mean change from baseline in absolute seizure rate, there is no suggestion of a therapeutic benefit of XR lamotrigine or placebo treatment for the whole study period. The XR lamotrigine group showed a mean 0.41 increase in seizure rate and the placebo group showed a 2.29 increase in seizure rate. For the whole study period, the arithmetic change from baseline in median seizure rate was a decrease of 2.11 for placebo and a decrease of 1.84 for XR lamotrigine. These analyses do not suggest any therapeutic benefit of XR lamotrigine in pediatric patients.

Listing 7.X
Listing of Weekly Seizure Frequency for All Partial Seizures
For Patients 16 Years of Age or Younger

Treatment	Center	Subj.	Age	Duration of Treatment (weeks)	Baseline Weekly Seizure Frequency	Treatment Period	Weekly Seizure Frequency
Placebo	007572	23	16	19	27.0	Escalation	(b) (4)
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	011396	1510	14	19	13.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	012925	1535	15	19	1.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021281	2125	15	19	4.8	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021491	1809	15	11	2.5	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
Lamictal	007572	22	14	19	16.3	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
Lamictal	008565	33	13	19	5.6	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	012925	1534	13	7	1.3	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
		1537	14	19	1.4	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	
	021281	2127	14	19	2.6	Escalation	
						Maintenance	
						Last 8 Weeks of Maintenance	
						Entire Treatment	

Reviewer Comment :

- Listing 7.X shows absolute seizure rates for baseline, the escalation period, maintenance period, and the whole study period for individual patients in each treatment group. The median reduction of seizure rate was 1.6 for XR lamotrigine and 0.4 for placebo, suggesting (but not clearly demonstrating) the possibility of some therapeutic benefit in

the XR lamotrigine group. The magnitude of this change for the whole study period was relatively small by this outcome measure.

One can also see from Listing 7.X that one patient (ID # 23) in the placebo group had a very high baseline seizure rate of (b) (4), that was much greater than the highest baseline rate (16.3) observed in the XR lamotrigine group. The placebo group also had another patient (ID # 1510) who had a relatively high seizure rate of (b) (4) that was similar to the highest rate in the XR lamotrigine group. Thus these data also show the uneven distribution of baseline seizure rate with lower seizure rates in the XR lamotrigine group.

Table 7.10B
Analysis of Investigator Global Assessment at the end of the study
For Patients 16 Years of Age or Younger

Clinical Factors	Treatment	n	Total Improvement	No Change	Total Deterioration	p-value [1]
Seizure Frequency	Placebo	4	2 (50%)	2 (50%)	0	0.4652
	Lamictal XR	4	3 (75%)	1 (25%)	0	
Seizure Duration	Placebo	4	0	4 (100%)	0	0.0285
	Lamictal XR	4	3 (75%)	1 (25%)	0	
Seizure Intensity	Placebo	4	0	4 (100%)	0	0.0285
	Lamictal XR	4	3 (75%)	1 (25%)	0	
Adverse Experiences	Placebo	4	0	4 (100%)	0	
	Lamictal XR	4	0	4 (100%)	0	
Social Functioning	Placebo	4	0	4 (100%)	0	0.0285
	Lamictal XR	4	3 (75%)	1 (25%)	0	
Intellectual Functioning	Placebo	4	0	4 (100%)	0	0.0285
	Lamictal XR	4	3 (75%)	1 (25%)	0	
Motor Functioning	Placebo	4	0	4 (100%)	0	0.1025
	Lamictal XR	4	2 (50%)	2 (50%)	0	
Overall Status	Placebo	4	1 (25%)	3 (75%)	0	0.1573
	Lamictal XR	4	3 (75%)	1 (25%)	0	

Reviewer Comment :

- Table 7.10B shows results for the global assessment of the investigator for improvement, no change, or deterioration. Overall, these results show an increased percentage of patients with positive therapeutic effects (including on seizure frequency, duration, and intensity) for XR lamotrigine treatment vs placebo treatment. These results are consistent with a therapeutic benefit of XR lamotrigine.

Listing 20B
Listing of Investigator's Assessment of Subject's Clinical Status
For Patients 16 Years of Age or Younger

Treatment	Center/ Subj	Visit	Study Day	Sz. Freq.	Sz. Dur.	Sz. Intens.	Adv. Exp.	Social Funct.	Intell. Funct.	Motor Funct.	Overall Status
Placebo											(b) (4)
Lamictal XR											

Note: 1=Marked deterioration, 2=Moderate deterioration, 3=Mild deterioration, 4=No change, 5=Mild improvement, 6=Moderate improvement, 7=Marked improvement

Reviewer Comment :

- I have looked at the investigator's overall status assessment for individual patients (Listing 20B) relative to the individual patient results for the primary efficacy endpoint for the entire treatment period (Listing 7.S). There 4 cases (patients # 1510 and 2125 for placebo; patients # 1537 and 2127 for XR lamotrigine) in which the investigator's assessment of the overall status appear to be reasonably good. However there were also 4 cases (patients # 23 and 1535 for placebo; patients # 22 and 33 for XR lamotrigine) in which there did not appear to be a good correlation. It is difficult to conclude that the investigator's overall status assessment of individuals is a reliable outcome measure.

Table 7.11B
Summary of Subject Satisfaction Questionnaire at the End of the Study
For Patients 16 Years of Age or Younger

Response	Placebo (N=5)	Lamictal XR (N=5)	p-value [1]
n	4	4	0.5134
Marked Improvement	0	1 (25%)	
Moderate Improvement	1 (25%)	1 (25%)	
Mild Improvement	1 (25%)	0	
No Change	2 (50%)	1 (25%)	
Mild Deterioration	0	0	
Moderate Deterioration	0	0	
Marked Deterioration	0	1 (25%)	

Reviewer Comment :

- Table 7.11B summarizes the results of the satisfaction questionnaire of individual patients. Overall, this analysis in only 8 patients (N=4/treatment) did not suggest a clear therapeutic benefit of XR lamotrigine treatment.

Listing 19B
Listing of Subject Satisfaction Questionnaire
For Patients 16 Years of Age or Younger

Treatment	Center	Subject	Visit	Seizure Control
Placebo	007572	23	Visit 8	No Change
	011396	1510	Visit 8	No Change
	012925	1535	Visit 8	Mild Improvement
	021281	2125	Visit 8	Moderate Improvement
Lamictal XR	007572	22	Visit 8	No Change
	008565	33	Visit 8	Moderate Improvement
	012925	1537	Visit 8	Marked Improvement
	021281	2127	Visit 8	Marked Deterioration

Reviewer Comment :

- I have looked at each patient's overall assessment in a satisfaction questionaire (Listing 19B) relative to the individual patient results for the primary efficacy endpoint for the entire treatment period (Listing 7.S). I thought that there was a reasonably good correlation of these outcome measures in 5 patients (patients # 1510, 1535, 2125 for placebo; patients # 33, 1537 for XR lamotrigine). In contrast, I thought that there was a poor correlation of these outcome measure in 3 patients. For placebo treatment, patient # 23 assessed " no change" despite a 60 % increase in seizure rate for the entire period. For XR lamotrigine treatment, patient # 22 assessed " no change" despite a 55 % increase in seizure rate for the entire period. However, more strikingly, patient # 2127, who was treated with XR lamotrigine, assessed "marked deterioration" despite a 96 % decrease reduction from baseline in seizure rate (i.e., almost complete resolution of seizures).

  Neither does this subjective outcome measure seem to be a good one for assessing the effect of treatment on seizure rate.

Safety Data

Table 8.A
Summary of Treatment-emergent Adverse Events
Subjects <= 16 Years of Age

System Organ Class Preferred Term	Placebo (N=5)	Lamictal XR (N=6)
ANY EVENT	4 (80%)	4 (67%)
Gastrointestinal disorders		
Any event	2 (40%)	3 (50%)
Diarrhoea	1 (20%)	1 (17%)
Abdominal pain upper	0	1 (17%)
Pancreatitis	0	1 (17%)
Vomiting	1 (20%)	0
Infections and infestations		
Any event	2 (40%)	1 (17%)
Measles	1 (20%)	0
Nasopharyngitis	1 (20%)	0
Tonsillitis	0	1 (17%)
Nervous system disorders		
Any event	1 (20%)	2 (33%)
Dizziness	0	2 (33%)
Drop attacks	1 (20%)	0
Somnolence	0	1 (17%)
General disorders and administration site conditions		
Any event	1 (20%)	1 (17%)
Irritability	1 (20%)	0
Pyrexia	0	1 (17%)
Respiratory, thoracic and mediastinal disorders		
Any event	1 (20%)	1 (17%)
Cough	1 (20%)	0
Pharyngolaryngeal pain	0	1 (17%)
Sinus congestion	0	1 (17%)
Eye disorders		
Any event	0	1 (17%)
Diplopia	0	1 (17%)

Reviewer Comment :

- Although Table 8.A shows summary results for 6 pediatric patients treated with XR lamotrigine, it is important to recognize that the actual safety experience was derived from only 5 patients because one of these patients discontinued from the study only 5 days after being randomized to treatment supposedly for the reason of "withdrawal of consent" according to the sponsor. Upon further inquiry the sponsor noted that : "We looked back at the CRF and there were no AEs or SAEs recorded for this subject. On the Investigator Comment log: "The patient refused visiting the site for the study completion procedures."" Nevertheless, I find this explanation puzzling and question why the site would note that the patient refused to come for completion of study procedures when the first required visit was not until 3 weeks after treatment and the patient had already experienced the procedures associated with collection of screening and baseline data. In my experience, I have rarely seen sites specify that a patient discontinued from the study for the reason of consent withdrawal or other when the real reason was because of an adverse event but the coding was not reported as such. Considering this extremely early study withdrawal, this patient did not actually provide any significant exposure

experience to the safety profile. Thus, for practical purposes, I consider the denominator in the safety experience for the XR lamotrigine group as N=5.

- Table 8.A shows that there was only one type of specific adverse event (dizziness) in more than one patient. There were 2 patients (2/5 = 40 %) treated with XR lamotrigine who experienced dizziness compared to no placebo patients who experienced dizziness (treatment effect/difference for XR lamotrigine % - placebo % = 40 %). In the same study (34) the treatment effect/difference for dizziness in adults was 14 %, a figure much lower than that for pediatric patients. This adverse event is a common one known to occur with lamotrigine treatment.

- I conducted a review of the label for immediate-release lamotrigine for randomized, double-blind, placebo-controlled studies in adults and pediatric patients for adjunctive treatment of epilepsy. The treatment effect/difference (XR lamotrigine % - placebo %) was 10 % in pediatric patients and 25 % in adult patients. In a fixed dose study in adults (taking an enzyme inducing AED and no valproate), the treatment effect/difference was 4 % for 300 mg daily, and 27 % for 500 mg daily.

- Although these results were derived from only 5 patients (in each group) treated with XR lamotrigine or placebo, the treatment effect/difference of 40 % seems somewhat higher than that for adults but also much higher than that for pediatric patients who were treated with immediate-release lamotrigine. It is also of interest that dizziness was also noted to be an adverse event associated with one pediatric patient who discontinued from the study during XR lamotrigine treatment. Nevertheless, because of the small number of pediatric patients studied during the investigation of XR lamotrigine, it is not possible to conclude that the risk for dizziness is clearly greater for treatment with XR lamotrigine compared to the risk for developing dizziness for treatment with immediate-release lamotrigine.

- It is difficult to suspect that the risk for any of the other specific adverse events occurring in only 1 XR lamotrigine-treated patient for several other adverse events is greater than that for placebo treatment.

Table 8.B
Summary of Treatment-emergent Serious Adverse Events
Subjects <= 16 Years of Age

System Organ Class Preferred Term	Placebo (N=5)	Lamictal XR (N=6)
ANY EVENT	1 (20%)	1 (17%)
Gastrointestinal disorders		
Any event	1 (20%)	1 (17%)
Pancreatitis	0	1 (17%)
Vomiting	1 (20%)	0
Nervous system disorders		
Any event	1 (20%)	0
Drop attacks	1 (20%)	0
Respiratory, thoracic and mediastinal disorders		
Any event	1 (20%)	0
Cough	1 (20%)	0

Reviewer Comment :

- Of note, one pediatric patient treated with XR had a serious adverse event, and this event was for acute pancreatic. Pancreatitis not listed in the lamotrigine label for the various clinical development programs but is listed as an adverse event that has occurred in the post-marketing experience. Nevertheless, pancreatitis is not considered to be a risk of treatment with lamotrigine.

The following is a narrative summary of the pediatric patient who developed pancreatitis.

Protocol Id: LAM100034
Investigator Number: 12926
Subject Number: 1534
Treatment Number: 89
Case Id: B0405460A
Suspect Drugs: Lamotrigine, Oxcarbazepine
Serious Events: Pancreatitis

This 13-year-old male subject was enrolled in a blinded study for the treatment of partial seizure. The subject received oral lamotrigine extended release 400mg daily from 28 December 2005 to 02 January 2006. The subject had started dose escalation on 15 November 2005.

Medical history included abdominal pain between April and September 2004 (at baseline). The abdominal pain had resolved spontaneously. Concomitant medications included oxcarbazepine. On 03 January 2006, six days after the start of lamotrigine, the subject presented with grade 2 or moderate possible pancreatitis. The event was disabling. He also experienced abdominal pain, vomiting, and dizziness. Laboratory examinations showed increased serum amylase (209 U/L) and increased alkaline phosphatase (956 IU/L) on 31 December 2005. The investigator reported that the subject had abdominal pain and vomiting for the last eight to nine days. The onset of the abdominal pain and vomiting was usually three to four hours after taking investigational product.

The dizziness lasted for five to six hours after taking investigational product. The abdominal pain, nausea and dizziness subsided approximately eight to ten hours after taking investigational product. The investigator reported that the subject had similar pain in the past when the dose of oxcarbazepine was increased. The pain had subsided following temporary reduction in dose of oxcarbazepine. The investigator also reported that the current abdominal pain was similar to the pain reported at baseline. The dose of lamotrigine was reduced on 4 January 2006 to 300mg. The event was unresolved at time of reporting. At the time of the report the pancreatitis was unconfirmed as the subject refused to undergo further investigations. Ultrasound was planned for 12 January 2006. The investigator considered that there was a reasonable possibility that the possible pancreatitis may have been caused by lamotrigine and that the event was possibly due to the concomitant medication, oxcarbazepine, and to the co-existing abdominal pathology. Follow up received 20 January 2006: Alkaline phosphatase at baseline was 268 U/L. Follow up received 7 February 2006: The subject received dose escalation of oxcarbazepine as per enzyme inducing anti epileptic drug due to a transcription error on the medication order form. The subject complained of pancreatitis six days after the week 7 escalation dose (subject received 400mg instead of 200mg). Follow up received on 02 August 2006: The subject was withdrawn from the study.

Reviewer Comment :

- On the basis of the above described information, I am not absolutely certain that this patient experienced acute pancreatitis. However, I think that the event described is consistent with possible acute pancreatitis and that it is possible that it was caused by XR lamotrigine treatment. Of note, there is no serum lipase level.

- I have requested additional information about this patient and the experience of pancreatitis and this information is pending.

- Pancreatitis is described in the post-marketing section of the labels for both lamotrigine and oxcarbazepine "pancreatitis and/or lipase and/or amylase increase"). Although I was unable to find any published reports of pancreatitis associated with oxcarbazepine treatment, I was able to find two cases ("Significant lamotrigine overdose associated with acute pancreatitis." J R Soc Med. 2009 Mar;102(3):118-9; "Acute pancreatitis associated with dual vigabatrin and lamotrigine therapy," Seizure. 1994 Dec;3(4):319) of pancreatitis associates with lamotrigine treatment.

Table 8.C
Summary of Adverse Events Leading to Withdrawal
Subjects <= 16 Years of Age

System Organ Class Preferred Term	Placebo (N=5)	Lamictal XR (N=6)
ANY EVENT	1 (20%)	1 (17%)
Gastrointestinal disorders		
Any event	1 (20%)	1 (17%)
Pancreatitis	0	1 (17%)
Vomiting	1 (20%)	0
Nervous system disorders		
Any event	1 (20%)	1 (17%)
Dizziness	0	1 (17%)
Drop attacks	1 (20%)	0
Somnolence	0	1 (17%)
Eye disorders		
Any event	0	1 (17%)
Diplopia	0	1 (17%)
Respiratory, thoracic and mediastinal disorders		
Any event	1 (20%)	0
Cough	1 (20%)	0

Reviewer Comment :

- As per Table 8.C, I believe that 4 adverse events (pancreatitis, dizziness, somnolence, diplopia) were recorded as adverse events leading to study withdrawal in one pediatric patient (# 1534) However, the adverse events of dizziness, somnolence, diplopia were not described as leading to study discontinuation in the narrative description of the adverse event of pancreatitis for patient 1534.

- I believe that vomiting, drop attacks, and cough were adverse events leading to study withdrawal at 11 weeks in one pediatric patient (#1809) treated with placebo.

The following Table 8.P shows some Blood Pressure outlier results for pediatric patients in Study 34.

Table 8.P
Incidence of Change from Baseline Outliers for Systolic BP, Diastolic BP, and Pulse
at Various Time Perspectives in DBP Study 100034
for Subjects <= 16 Years of Age

Vital Sign	Treatment	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
SBP Inc>=20	LTG	1/ 5 (20%)	1/ 5 (20%)	1/ 4 (25%)	1/ 4 (25%)	1/ 4 (25%)
SBP Inc>=20	Placebo	0/ 5 (0%)	0/ 5 (0%)	0/ 5 (0%)	0/ 4 (0%)	0/ 4 (0%)
SBP Inc>=20	Rx Effect	20%	20%	25%	25%	25%
SBP Inc>=40	LTG	0/ 5 (0%)	0/ 5 (0%)	1/ 4 (25%)	0/ 4 (0%)	0/ 4 (0%)
SBP Inc>=40	Placebo	0/ 5 (0%)	0/ 5 (0%)	0/ 5 (0%)	0/ 4 (0%)	0/ 4 (0%)
SBP Inc>=40	Rx Effect	0%	0%	25%	0%	0%
DBP Inc>=10	LTG	1/ 5 (20%)	1/ 5 (20%)	1/ 4 (25%)	1/ 4 (25%)	1/ 4 (25%)
DBP Inc>=10	Placebo	0/ 5 (0%)	0/ 5 (0%)	0/ 5 (0%)	0/ 4 (0%)	0/ 4 (0%)
DBP Inc>=10	Rx Effect	20%	20%	25%	25%	25%
DBP Inc>=20	LTG	1/ 5 (20%)	1/ 5 (20%)	1/ 4 (25%)	1/ 4 (25%)	0/ 4 (0%)
DBP Inc>=20	Placebo	0/ 5 (0%)	0/ 5 (0%)	0/ 5 (0%)	0/ 4 (0%)	0/ 4 (0%)
DBP Inc>=20	Rx Effect	20%	20%	25%	25%	0%
SBP Dec<=20	LTG	1/ 5 (20%)	0/ 5 (0%)	0/ 4 (0%)	1/ 4 (25%)	0/ 4 (0%)
SBP Dec<=20	Placebo	1/ 5 (20%)	0/ 5 (0%)	0/ 5 (0%)	0/ 4 (0%)	0/ 4 (0%)
SBP Dec<=20	Rx Effect	0%	0%	0%	25%	0%

Reviewer Comment :

- There was one patient treated with XR lamotrigine who experienced a modest increase (≥ 20 mm Hg) in systolic blood pressure (SBP) from baseline/pre-treatment at all visits and one severe SBP increment (≥ 40 mm Hg) at visit 6. Outlier BP criteria not shown were not presented because there were no remarkable results prompting presentation or comment.

- There was one patient who experienced a modest increase (≥ 10 mm Hg) in diastolic blood pressure (DBP) from baseline/pre-treatment at all visits and a more severe DBP increment (≥20 mm Hg) at most visits.

- Upon my inquiry, I learned that one patient (# 22), who was treated with XR lamotrigine (200 mg daily dose) and VPA and levetiracetam accounted for these increased blood pressure outlier results noted above here. These blood pressure increments occurred in the 14 year old patient was who very thin (24 kg, 53 lbs) and whose serum lamotrigine were considered very high for the prediction for this patient according to the PK model. Additional details regarding this patient and his PK samples were outlined and described earlier in PK section for pediatric patients.

- The following table shows the absolute SBP and DBP results and the increments from baseline/pre-treatment for this patient.

Table Blood Pressure Results and Change from Baseline for Patient #22

Study Visit	SBP	SBP Increase from Baseline/Pre-treatment	DBP	DBP Increase from Baseline/Pre-treatment
Baseline/Pre-treatment	(b) (4)			
Visit 4/3 weeks				
Visit 5/7 weeks				
Visit 6/11 weeks				
Visit 7/15 weeks				
Visit 8/19 weeks				

- These increments in SBP and DBP are quite impressive to me. I think that it is possible that blood pressure increments were caused by XR lamotrigine treatment. At baseline this patient had a relatively low SBP and DBP but I would still consider these values to be consistent with "normal." Although this patient did not have an adverse event for blood pressure increase, these increments are significant.

  It is not clear that lamotrigine treatment causes blood pressure changes as per its label. Although analyses of outlier results for all patients in study 34 showed some instances of increased and decreased blood pressure at different times for XR lamotrigine treatment (vs placebo), there was no clear demonstration of a consistent alteration in SBP or DBP. In outlier vital sign (VS) analyses of a "Thorough" QTc Study of healthy volunteers, there was some subtle suggestions that DBP may be modestly increased ($\geq$ 10 mm Hg) DBP, but these effects were not clear and unequivocal. In this study, patients were randomized to placebo or immediate-release lamotrigine and were studied for orthostatic VS (supine and standing) at different times during the study when patients received 100 mg daily lamotrigine (at 6 weeks), 300 mg daily lamotrigine (at 9 weeks), and 400 mg daily lamotrigine (at 11 weeks). All these results were potentially confounded by treatment duration and dose during which different lamotrigine doses were studied after different treatment durations.

- Although it is difficult to exclude the possibility that this patient's significant SBP and DBP increments were related to XR lamotrigine treatment, it is difficult to be very confident that they related to XR lamotrigine. The time course for showing the blood pressure increments was consistent lamotrigine treatment but they were not clearly dose-

related. If the blood pressure increments, were related to XR lamotrigine treatment, it may be because this patient was so very thin and underweight and that the serum lamotrigine levels observed in this patient were relatively high for such a low weight patient (24 kg, 53 lbs).

Reviewer's Overall Assessment of PK, Efficacy, and Safety of XR Lamotrigine in Pediatric Patients (13-16 years old)

Reviewer Comment :

- Overall, I think that the PK, efficacy, and safety data collected in study 34 are inadequate/insufficient in pediatric patients (13-16 years old) to approve XR lamotrigine for treatment of adjunctive partial seizures.

- I have noted my interpretations of the limited pediatric data collected and my cautions, caveats, and potential concerns. Although there may be suggestions of efficacy, it is not clear. There is a question in my mind if the PK levels in these patients may be somewhat higher than that in older adults and there were some safety experiences that stood out in these few pediatric patients.

- I note that the sponsor could have tried to ensure the more study of adequate numbers of pediatric patients in the age group of 13-16 years by stratifying randomization in this age group to try to collect adequate PK, efficacy, and safety data. However, the sponsor did not implement this strategy for collecting more adequate data in this age group to support the approval of use for this age group.

- I recommend that the sponsor collect additional information in this pediatric age range.

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/s/

Leonard Kapcala
5/29/2009 02:47:45 PM
MEDICAL OFFICER

Norm, Here is my review. Please let me know
if any questions and sign. Thanx. Len

Norman Hershkowitz
5/29/2009 02:50:02 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA: 20-241, 20-764, 22-115, 22-251
Sponsor: Glaxo SmithKline
Drug: Lamotrigine (Lamictal®)
Material Reviewed: Proposed labeling and Medication Guides
Subject: Anticonvulsant-associated suicidality
Reviewer: Marc Stone, M.D.
Submission Dates:
Date Review Completed:

The Division asked the manufacturers of all antiepileptic drugs to submit labeling language and Medication Guides that discuss the risk for suicidal thoughts and behaviors associated with the use of these medications. The Division's request was based on the results of a meta-analysis of randomized, placebo-controlled controlled, clinical trial data that found an increased risk of suicidal thoughts and behaviors with antiepileptic drugs. The Division specifically requested class labeling, including a WARNING statement or WARNINGS and PRECAUTIONS statement for PLR labels, an Information for Patients statement, as well as a Medication Guide, and a Risk Evaluation and Mitigation Strategy (REMS). The Division also asked manufacturers to include language informing prescribers and patients about the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This memo reviews GSK's response to the Division's request for their antiepileptic drug, lamotrigine (Lamictal®).

There was some discussion concerning how to integrate warnings concerning suicidality both into labeling and into a comprehensive Medication Guide. Current labeling for lamotrigine contains a boxed warning about the risk of severe skin reactions including Stevens-Johnson syndrome. There are also substantial concerns with hypersensitivity reactions, multiorgan failure and blood dyscrasias. (b) (4) In addition, it was decided that long-time concerns over name confusion between Lamictal® and other drugs, particularly Lamisil®, causing medication errors merited provision of specific information in the Medication Guide intended to assist patients in identifying and avoiding this problem. With integration of these changes, the labeling, Medication Guide and REMS appear to be satisfactory.

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/s/

Marc Stone
4/23/2009 11:39:42 AM
MEDICAL OFFICER

Sally Yasuda
4/23/2009 11:54:16 AM
INTERDISCIPLINARY

CLINICAL REVIEW of NDA

Application Type	NDA
Submission Number	22115
Submission Code	N 000
Letter Date	11/22/06
Stamp Date	11/22/06
PDUFA Goal Date	9/22/07
Reviewer Name	Leonard Peter Kapcala, M.D.
Review Completion Date	9/14/07
Established Name	lamotrigine XR
(Proposed) Trade Name	Lamictal XR
Therapeutic Class	Anticonvulsant
Applicant	GlaxoSmithKline (GSK)
Priority Designation	S
Formulation	XR = extended release
Dosing Regimen	Oral, once daily
Indication	Treatment of Adjunctive Partial Epilepsy
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- I recommend an approvable action because I cannot clearly conclude that XR lamotrigine is effective for adjunctive treatment of partial epilepsy in adults. The sponsor needs to address adequately the reason that XR does not appear to be effective in U.S. patients (that comprised nearly 40 % of all randomized patients) and why there should not be an Agency concern that the demonstration of efficacy is driven by solely foreign data in the sole pivotal study designed to demonstrate efficacy of XR lamotrigine.

    - If the sponsor cannot adequately explain the lack of efficacy in U.S. patents and address and satisfy Agency concerns, the sponsor should conduct another pivotal efficacy study either solely in the U.S. and/or in other locations (e.g. Canada, western European countries) in which the Agency generally has confidence in the quality of clinical data collection.

    - The results of the pending DSI inspections of 2 Korean sites have not yet been received (as of 9/14/07). However, the recently received (9/14/07) communication (9/10/07 cover letter) from the sponsor describing several, various errors (including efficacy seizure rate data) in transcribing source data to CRFs raises serious questions about the quality of data not only at these 2 foreign sites but also at potentially many other foreign sites.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

- Not applicable at this time

1.2.2 Required Phase 4 Commitments

If XR lamotrigine is approved for adults (≥ 16 years), I believe that the sponsor should make a phase 4 commitment to develop and study XR lamotrigine in pediatric patients. The present NDA does not support the efficacy and safety of XR lamotrigine in any pediatric patients (< 16 years). (b) (4) The main question is what should be the lower pediatric age limit for this development of the XR formulation?

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

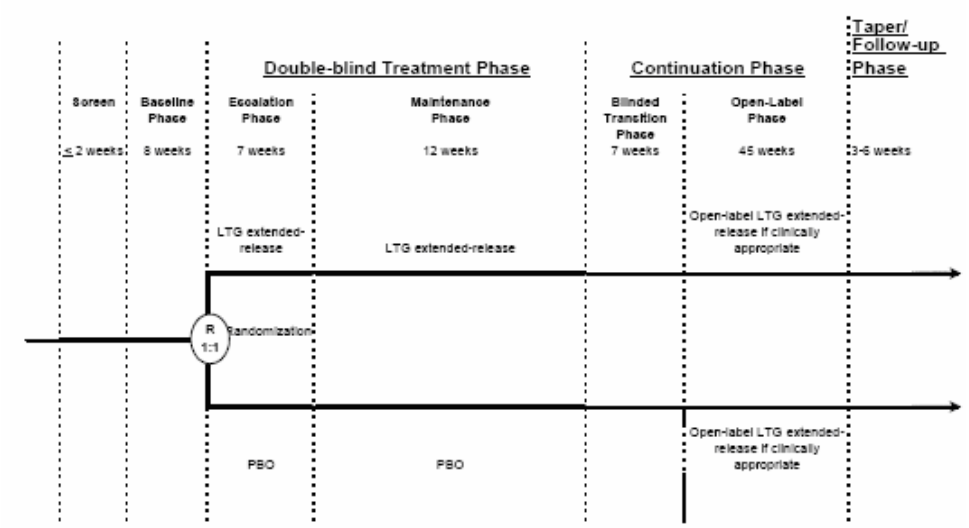
Lamotrigine extended-release (XR lamotrigine) is a new, enteric coated, formulation for a once daily dosing regimen. The clinical development program for XR lamotrigine consists of seven Phase I Clinical Pharmacology studies conducted in healthy volunteers (LAM10007, LAM10004, LAM10005, LAM100014, LAM100017, LAM105537 and LAM102611). In addition, one important short-term study (LEP103944) conducted in patients with epilepsy evaluated the pharmacokinetics and safety experience of patients who were converted from immediate release (IR) lamotrigine to XR lamotrigine and then back to IR lamotrigine. The main clinical pharmacology studies mainly evaluated the single and multiple dose pharmacokinetics, dose proportionality, dosage strength equivalency, food effect and the conversion from the immediate release dosage form to the proposed extended release dosage form and a drug interaction study with esomeprazole. The other studies were exploratory and formulation development in nature.

In addition to these studies, blood samples for population pharmacokinetic (PK) analysis were collected in one pivotal, (Phase III) randomized, double-blind, placebo-controlled Clinical Study evaluating the efficacy and safety of XR lamotrigine as adjunctive treatment for partial seizures in patients 13 years of age and older (LAM100034). The study population consisted predominantly of patients taking concomitant valproic acid (VPA) or enzyme-inducing anti-epileptic drugs (EIAEDs) or "neutral" AEDs (AEDs that do not alter plasma lamotrigine levels). A thorough QTc study was also conducted using the IR dosage from.

1.3.2 Efficacy

The only randomized, double-blind, placebo-controlled study (LAM100034) supporting approval of XR lamotrigine randomized and treated (as adjunctive therapy with $\geq$ 1 anti-epileptic drug – AED) patients ($\geq$ 13 years, but mostly adults $\geq$ 16 years) with partial seizures over a period up to 19 total weeks after a prospective baseline seizure rate collection period ranging from 4-8 weeks. The schematic diagram of the study design is provided here.

Schematic Diagram of Study LAM100034



Although study LAM100034 showed that XR lamotrigine was statistically superior to placebo (see table below) for the primary analysis of the primary efficacy endpoint (median reduction in percentage of partial seizure rate from baseline), there was no suggestion of efficacy in patients treated in U.S. sites (see additional table below).

Primary Analysis of the Median Percent Reduction in Partial Seizure Frequency During the Entire Treatment Phase (ITT Population: Study LAM100034)

All Partial Seizures (A-C)	PBO N=120	LTG XR N=116
n	120	116
Median (Range)	24.2 (-231, 100)	46.1 (-177, 100)
Estimated Difference[1]	18.17	
95% CI for Difference[1]	8.301, 28.025	
p-value[1]	0.0004	

Data Source: Table 7.1, Table 7.2

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

Primary Efficacy Endpoint for ALL Randomized Patients for U.S. Sites vs All Foreign Sites as a Pooled Group and According to Each Foreign County

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

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

Numerous, sensitivity analyses of efficacy were robust in clearly supporting the observation that XR lamotrigine is highly effective in foreign sites/patients but not in U.S. sites/patients, who contributed nearly 40 % of the efficacy data. The absence of data suggesting at the least, reasonable, numerical efficacy in U.S patients is a serious concern precluding the overall conclusion that XR lamotrigine is effective as adjunctive treatment of partial seizures in adults. The concern about the demonstration of efficacy (based upon the lack of efficacy in U.S. patients) was not allayed by the efficacy demonstrated in foreign sites/patients because the vast majority of foreign patients were treated in locations (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina) for which we do not have adequate/sufficient experience to be confident in the quality of clinical data collected.

The statistical reviewer also made an important observation related to the facts that the sponsor over-enrolled (by ~ 52 %) and over-randomized (~ 84 %) more patients than had been planned as per the protocol (see Statistical Review for more details and Reviewer Comments toward the end of section 6.1.4 Efficacy Findings). These increased numbers occurred without a protocol amendment. The protocol had planned to enroll 204 patients in order to obtain 132 randomized patients total based on an assumed baseline dropout rate of 35%. However, a much larger number (N=308) was enrolled and nearly twice as many patients (N=243) were randomized. The

sponsor suggested that this occurred because it did not closely monitor enrollment and randomization.

I consider the pending results of DSI inspections of 2 Korean sites (not received as of 9/14/07) as potentially capable of being a surrogate concern signal for all foreign data and potentially capable of providing a reason questioning the validity of the foreign data as a whole (pending other potential DSI inspections of other foreign sites).

Of significant concern,, shortly prior to the PDUFA action date, on 9/14/0 I received a sponsor communication (9/10/07 cover letter) noting that its internal, quality control inspection of the 2 Korean sites scheduled for DSI inspection had identified several, various errors (including errors related to seizure rate efficacy data) in transcribing information from source documents to CRFs at both Korean sites. This letter is presented in section 4.4 (Data Quality and Integrity).

It does not seem possible to assess yet how important **these problems/errors/deficiencies detected BY THE SPONSOR** at both of these Korean sites are. However, these discrepancies/errors related to seizure data collection certainly raise a potential red flag not only about data (especially efficacy data) collected at these Korean sites, but also potentially at many other foreign sites not yet inspected (nor planned at this time for inspection) by anyone. Nevertheless, from this reviewer's perspective. this sponsor communication raises more questions about the quality of the foreign data collected (especially in the foreign sites collected outside of Germany).

Reviewer Efficacy Conclusion

- **I am unable to conclude that XR lamotrigine is effective as adjunctive treatment of partial epilepsy in adults based upon my concerns outlined about the lack of efficacy with U.S. data and questions about the quality of the foreign data that drive the demonstration of efficacy.**

1.3.3 Safety

There is no clear evidence that the safety profile for XR lamotrigine treatment is different than that recognized for IR lamotrigine treatment.

There may be some relatively minor differences in the overall safety profile (relative to types of TEAEs and the period of greatest risk for these TEAEs) of XR lamotrigine treatment vs that for IR lamotrigine treatment. However, it is not clear that the relatively minor differences may be related to the analyses conducted in this NDA vs analyses previously conducted for IR lamotrigine.

Nevertheless, I have concerns and suspicions that lamotrigine may produce notable changes in vital signs that may warrant description in the label. However, analyses of vital signs for studies LAM100034 and SCA104648 are not appropriate and additional analyses (especially for

outliers) should be requested. My concerns about vital sign analyses are outlined in sections 7.1.8 and 7.1.12.

Reviewer Safety Conclusion

- **Although the safety profile for XR lamotrigine does not appear to exhibit major differences from the safety profile recognized for IR lamotrigine, I believe that additional analyses of vital signs should be requested of the sponsor in an approvable letter because results from these analyses may warrant description in the lamotrigine label.**

1.3.4 Dosing Regimen and Administration

The dosing regimen for XR lamotrigine (recommended by this reviewer) in patients initiating treatment with lamotrigine is shown below in the following table.

Escalation Regimen for LAMICTAL XR in Patients ≥ 16 Years of Age

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance Range (Week 8 and onward)	200-250 mg every day	200-400 mg every day	400-600 mg every day

* Rifampin and estrogen-containing estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

1.3.5 Drug-Drug Interactions

Major drug-drug interactions (DDIs) between IR lamotrigine and certain concomitant AEDs (e.g. EIAED that significantly reduces lamotrigine exposure and VPA that significantly increases lamotrigine exposure) are well known and sufficiently characterized. XR lamotrigine shows a generally similar DDI with these concomitant AEDs as does IR lamotrigine.

There are no new DDIs that have been identified with the exception that esomeprazole (proton pump inhibitor), that raises gastric pH slightly, lowers XR bioavailability (~ 12 % decreased AUC) by a relatively small degree compared to that for IR lamotrigine. This relatively small effect is not likely to have an important clinical impact on most patients treated with XR lamotrigine. However, I am concerned that this DDI could potentially have a clinically significant impact on a subgroup of certain patients (e.g. those using one or more concomitant EIAEDs). I noted this potential DDI interaction concern because EIAEDs have the potential for a considerable (~ mean 50 %) reduction in AUC on IR lamotrigine compared to patients not using EIAEDs and ~ a mean 21 % reduction of XR vs IR bioavailability. In addition, some individual patients using concomitant EIAEDs with XR lamotrigine have the potential for a much more marked decrease in bioavailability (vs IR) as reflected by a decrease in AUC up to ~ 50 % and decrease in Cmax up to ~ 60 %. I believe that a caution should be noted in the label that patients treated with XR lamotrigine and one or more concomitant EIAEDs in conjunction with a proton-pump inhibitor (or drug that can raise gastric pH) should be monitored to determine whether the dose of XR lamotrigine should be increased because of inadequate seizure control.

1.3.6 Special Populations

There are no comments here other than the facts that the label should note that XR is indicated for treatment of adult patients ($\geq$ 16 years) with partial epilepsy and that there is little experience with treating elderly patients (> 65 years) with XR lamotrigine.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor noted that LAMICTAL® (lamotrigine, LTG), a phenyltriazine anticonvulsant, was first approved in the US in December 1994 (NDA 20-241) for adjunctive treatment of partial seizures in adults. Subsequent to this approval, LAMICTAL was approved in August 1998 for adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in pediatric (2-16 years of age) and adult subjects (along with a chewable dispersible tablet formulation; NDA 20-764), in December 1998 for conversion to monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug (EIAED), and in January 2003 as adjunctive treatment for partial seizures in pediatric subjects (2-16 years of age). LAMICTAL was approved in June 2003 for long-term management of mood episodes in subjects with Bipolar I disorder and in January 2004 for conversion to monotherapy from valproate (VPA) in adult subjects with partial seizures. Most recently, LAMICTAL was approved for primary generalized tonic-clonic (PGTC) seizures in September 2006 in adults and pediatric subjects (2-16 years of age).

Lamotrigine is currently marketed as immediate-release compressed or chewable dispersible tablets (lamotrigine IR). The current dosing recommendations in the US for lamotrigine IR are twice daily for concurrent administration with EIAEDs or as monotherapy and once or twice daily administration with valproic acid (VPA). Lamotrigine extended-release (lamotrigine XR) is a new, enteric coated, formulation that may allow subjects with seizures to be on a once daily dosing regimen. Lamotrigine XR slows the dissolution rate of lamotrigine by releasing 80% of drug over a period of 12-15 hours, compared to a 15 minute time period for lamotrigine IR. This results in a slower rate of absorption, a reduction in the peak to trough fluctuations and fewer fluctuations in lamotrigine concentrations over a 24-hour interval for lamotrigine XR, compared to lamotrigine IR. Administration of lamotrigine XR compared to lamotrigine IR may improve compliance due to once a day as opposed to twice a day dosing [Cramer, 2002; Doughty, 2003].

This Clinical Overview provides an overall summary of the efficacy, safety and pharmacokinetics of lamotrigine extended-release (lamotrigine XR) tablets as adjunctive therapy in the treatment of partial seizures in subjects ≥13 years of age. This application is based on a single pivotal clinical study (LAM100034) along with an additional study (LEP103944) to support conversion from immediate-release (IR) to extended-release (XR) lamotrigine. The remaining pharmacokinetic studies involved healthy subjects. As such, there was no integration of efficacy data and little integration of safety data. Thus, separate integrated analyses of efficacy and safety were not produced for this submission. A summary of the clinical development program is provided in Section 1.5.

Nature of the Disease

Epilepsy is one of the most common chronic neurological disorders in children and adults. An epileptic seizure consists of repetitive, synchronous discharges of a population of neurons in the brain which may have associated motor, sensory or autonomic clinical correlate. Epilepsy is commonly diagnosed after 2 or more unprovoked seizures separated by at least 1 day. Provoked

seizures are those which occur in the setting of an acute neurological insult or systemic disorder, such as head trauma, brain tumor, cerebrovascular malformation, central nervous system infection or toxic/metabolic conditions. Seizures caused by a known lesion or abnormality of the brain are called symptomatic epilepsy. Epilepsy for which no cause can be determined is called idiopathic and is commonly found to be inheritable or genetic in origin. When no cause or etiology of the seizures can be determined, but the epilepsy is thought to be symptomatic, it is called cryptogenic. Although the diagnosis of epilepsy is based on clinical features, ancillary testing including electroencephalography and neuroimaging of the brain (cranial computed tomography, magnetic resonance imaging) often provide supportive or confirmatory data.

Under the International Classification of Epileptic Seizures [Commission, 1981], seizures are further classified as either partial (focal, localization related) or generalized. Partial seizures arise from one area of the brain, and they are further subdivided into simple, in which awareness and memory are preserved (also called an aura) or complex, where there is transient alteration of awareness and memory. The clinical behavior that is associated with a partial seizure is dependent upon the area of the brain where the seizure began as well as the propagation of the ictal discharge to other areas of the brain. Partial seizures that spread to involve both cerebral hemispheres and have associated clonic motor activity are called secondarily generalized seizures. Conversely, generalized seizures arise from both cerebral hemispheres simultaneously, and they have no lateralizing or focal clinical manifestations. Generalized seizures are further subdivided based on ictal semiology into absence, myoclonic, clonic, tonic, tonic-clonic and atonic. Typically, seizures of both types last 5 minutes or less. However, prolonged seizures of either type may occur, and seizures that last 30 minutes or longer are called status epilepticus [Working Group on Status Epilepticus, 1993].

The incidence of epilepsy has a bimodal distribution with peaks in the first year of life and in the elderly, with an overall prevalence of 0.5 to 1% of the population (approximately 2.7 million individuals) [Hauser, 1975; Aziz, 1994; Epilepsy Foundation, 2006]. Generalized seizures comprise 50% of all seizures in children, but in adults, partial seizures occur more commonly, estimated at 70% of all seizures [Hauser, 1992]. Status epilepticus is the presenting seizure in as many as 5% of patients with epilepsy, and up to 16% of all patients with epilepsy will have at least one episode of status epilepticus during their life [Hauser, 1990]. Patients that have a history of a prolonged seizure or status epilepticus are more likely to have recurrence of a prolonged seizure or status epilepticus [Shinnar, 2001].

Multiple factors are posited to be required to result in the pathogenesis of the hyperexcitable state that culminates in an epileptic seizure. Three key elements have been hypothesized: the capability of cellular membranes of pacemaker neurons to develop intrinsic bursts discharges, a reduction in GABA inhibition and enhancement of excitation through neuronal circuits [Prince, 1986]. However, the actual pathogenic mechanisms of epileptigenesis and the clinical condition of epilepsy are varied and the details are not known. Although most antiepileptic drugs (AEDs) have one or more documented mechanisms of action which might control or reduce seizure frequency and severity, the exact mechanism of action is similarly not known.

Patients with epilepsy have significantly increased morbidity, including closed head injury, fractures, burns, dental injury and soft tissue injury [Spitz, 1998; Wirrell, 2006]. There is also suspected decline in or worsening of memory, cognition, depression and sexual function. Additionally, increased mortality rates have been reported in patients with epilepsy, some of which may be attributable to the underlying cause of the epilepsy [Rafnsson, 2001; Camfield, 2002]. In adult patients presenting with status epilepticus, mortality has been reported as high as 19% [DeLorenzo, 1999].

2.2 Currently Available Treatment for Indications

Pharmacological therapy is the initial option for treatment of patients with newly diagnosed epilepsy. The exact mechanism of action is not known for currently approved AEDs. Potential mechanisms of action include modulation of voltage-gated sodium ion channels (sodium and calcium), enhancement of inhibitory neurotransmission (GABA) or attenuation of excitatory neurotransmission (glutamate) [Rogawski, 2004]. Many AEDs may have multiple potential mechanisms of action, while some have mechanisms which remain unclear. The goal of medical therapy is to have complete seizure control without side effects. Monotherapy is preferable to polytherapy, since this limits drug-drug interactions and reduces side effects [Karceski, 2005]. The ideal AED should have broad spectrum, be suitable for all patient groups, have limited drug-drug interactions, a therapeutic starting dose, appropriate formulations for children and adults, and a long half-life [Wallace, 2001]. Drugs with longer half-lives are generally associated with reduced peak to trough fluctuations in drug concentrations. It is commonly believed that there is an optimal serum concentration for each AED, with toxicity occurring when significantly above this concentration and seizures occurring when significantly below this concentration. However, this optimal concentration may vary from patient to patient, hence the need for individualized titration.

Nine AEDs (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, and pregabalin) have been approved in the US since 1993 for adjunctive therapy in partial epilepsy. There is no evidence that the newer AEDs are more effective than the older AEDs (phenobarbital, phenytoin, carbamazepine, and valproic acid), but the newer AEDs tend to be better tolerated than the older AEDs [Kwan, 2000]. Despite medical therapy, 60 to 70% of all patients with epilepsy continue to have seizures which are refractory to multiple trials of AEDs [Kwan, 2000]. Patients are considered medically refractory when they fail to have seizure control after treatment with 2 or more AEDs and they have had epilepsy for 2 or more years. These individuals may then be candidates for alternative treatments, including epilepsy surgery, vagus nerve stimulator or direct brain stimulation. However, the majority of these patients continue to have refractory seizures, with only epilepsy surgery for temporal lobe epilepsy having been demonstrated to be superior to maximal medical therapy in medically refractory patients [Wiebe, 2001].

The majority of AEDs currently approved for adjunctive treatment of partial seizures require multiple daily dosing because of inherently short half-lives and/or drug interactions which result in increased clearance of the drug. Thus, availability of extended-release formulations would be desirable, since requirements for multiple daily

dosing may be a factor in decreased compliance. Medication compliance has been shown to be an important factor in seizure control, with 40 to 50% of seizures in patients with epilepsy being associated with medication non-compliance [Cramer, 2002; Specht, 2003; Jones, 2006]. Medication non-compliance has been reported in several studies to be one of the most common causes of status epilepticus [Aminoff, 1980; Lowenstein, 1993; DeLorenzo, 1996]. With each increase in dose frequency from one, two, three or four times daily, missing a dose of medication increased the likelihood of a seizure by 36% [Cramer, 2002]. Therefore, factors which are associated with increased medication compliance should be associated with improved seizure control and reduced seizure severity. Extended-release AEDs have been demonstrated to have improved tolerability due to a reduction in side effects [Smith, 2004; Ficker, 2005]. Improved efficacy was also demonstrated with one extended-release AED, which was felt to be due to either improved medication compliance or decreased serum concentration fluctuations [Ficker, 2005].

Currently there are only three AEDs (carbamazepine, phenytoin, and valproate) for which an extended-release formulation is available. Therefore, additional treatment options that allow once-daily dosing are needed.

2.3 Availability of Proposed Active Ingredient in the United States

Lamotrigine (Lamictal) is an approved drug for several indications as outlined in the Introduction in section 2.1.

2.4 Important Issues With Pharmacologically Related Products

There are no issues worthy of comment because there are no drugs that are pharmacologically related to lamotrigine and which are approved in the U.S.

2.5 Presubmission Regulatory Activity

The following is an abstract of the Pre-NDA meeting (5/25/06) held between the DNP and the sponsor (GSK).

"Meeting Purpose
This purpose of this meeting is to discuss the content and format of a New Drug Application to support an indication for adjunctive treatment of partial seizures in patients 13 years of age and older.

Pre-meeting Minutes
1. Does the Agency agree with GSK's proposals to address the degradation impurity identified during formulation development?
Agency Response: No. We recommend that you qualify the degradant, investigate more protective blister packaging, or propose an appropriate expiration dating period for the current blister presentation.

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

A pediatric waiver has not been granted since this new dosage form (extended release formulation) is likely to be used for a substantial number of pediatric partial seizure patients younger than age 13. Therefore, a pediatric assessment is required under the Pediatric Research Equity Act (PREA). The requirement for data in a younger population can be deferred.

In addition to the studies mentioned the sponsor should also provide dissolution data in the CMC section.

3. Does the Agency agree with GSK's proposal regarding reduction of the sample size of supportive study LEP103944, an open label study evaluating the conversion from immediate release to extended release lamotrigine?
Agency Response: Given the fact that the sponsor intends to pool the sparse sample data from Study LAM 100034, a total of 8 subjects in this study should be reasonable. A description of study LAM 103944 in labeling has the potential to imply therapeutic equivalence between the immediate release and extended release formulations. This needs to be considered in discussing this study.

4. Does the Agency agree that safety information from clinical trials with lamotrigine immediate-release tablets can be used to support the safety of lamotrigine extended release tablets?
Agency Response: Yes

5. Does the Agency agree that results of an ongoing study evaluating the effects of lamotrigine on the QT/QTc interval can be submitted in the 120 day safety update?
Agency Response: Yes

6. Does the Agency agree with GSK's proposals for the analysis of safety information from the lamotrigine extended release clinical development program?
Agency Response: Yes, but, additionally, any serious adverse effects from the treatment period of study LAM 100036 should also be included along with the LAM 100036 unblinded continuation data in the ISS.

7. Does the Agency agree with GSK's proposal for use of the Clinical Overview as the primary summary of efficacy and safety data for the lamotrigine extended release tablets clinical development program?
Agency Response:
Yes, this is acceptable.

Additional Clinical Pharmacology Comments :

• Dose dumping with alcohol should be evaluated. First, in vitro dissolution studies in various concentrations of alcohol (e.g. 5, 10, 20 and 40%) should be conducted. Once results are available, the sponsor should discuss this with the Office of Clinical Pharmacology for assessing the need for in vivo study.

• Outline of the summary section of the HPBIO section is provided. At the time of NDA submission the sponsor can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically (Document attached)

Meeting Discussion

• The division has reviewed proposals similar to the submitted degradation impurity proposal from GSK, and they have consistently set specifications based on ICH thresholds for the maximum daily intake. GSK's specifications are a problem if people use multiple 25 mg or 50 mg tablets to achieve a higher dose.

• GSK stated that the blister pack was still within ICH limits based on the daily doses that would be administered during dose titration. However, the division said they never set specifications based on titration. The division is concerned with having different specifications for the blister packs and the bottles and for the low versus higher strengths.

• GSK questioned whether there was specific concern regarding the toxicity of this degradant. There is no specific concern based on the possible structures for the impurity. They also wondered if the division had any thoughts on how they should qualify the degradant. The nonclinical studies needed to qualify the degradant are those referred to in the ICH impurities guidance Q3B(R); i.e., studies of in vitro genotoxicity, general toxicity in one species (3 months duration for chronic indications), and embryofetal developmental toxicity in one species, designed to allow comparison of unqualified to qualified material.

• The division would expect the qualification with the initial NDA submission.

• GSK inquired about the Agency's rationale for choosing 40% alcohol as well in the in vitro study. The division responded that the rationale was to look at the worst case scenario. GSK also inquired that, if no interaction is seen up to the 20% alcohol concentration, but only at 40% alcohol concentration, what would the Agency's conclusions on this observation be. The division said that they will take this into consideration in the overall decision. GSK also inquired about the dissolution media pH in which the dissolution studies should be conducted. The division responded that they should conduct these studies in the proposed dissolution media (that is optimal) for the product. GSK inquired that if an in vivo study would be needed based on the in vitro results, could this be submitted during the review cycle. The division responded there can be room for negotiation given that our policy on alcohol interaction studies is evolving, although in most cases it tends to delay the review cycle depending on when the information was submitted.

• Regarding question number 6, from above, the division clarified that the safety data from the blinded and unblinded studies should not be merged.

• The division is concerned with leaving patients unprotected when switching to ER from IR and the implication of therapeutic equivalence that might result from putting the conversion study in labeling. They do not want to imply in labeling that patients will have the same degree of seizure control when converting. GSK said that in the NDA submission, they will provide an argument

regarding the kinetics of the extended release formulation in patients on concomitant antiepileptic medications that are enzyme inducers and inhibitors.
• GSK is planning to submit the NDA in November 2006.
• GSK will need to submit a pediatric development plan with the NDA. If it is impossible to make an extended release tablet or liquid that a child may take, GSK should make that argument.

2.6 Other Relevant Background Information

Sponsor's Rationale for the Development of Lamotrigine XR for Adjunctive Treatment of Partial Seizures

The effectiveness of lamotrigine IR as add-on therapy in treating adult subjects with partial seizures was demonstrated in ten placebo-controlled studies; nine were crossover design studies (N=338 subjects) and one was a parallel design study (N=191 subjects). Eight of the nine crossover studies showed a statistically significant reduction in the frequency of all partial seizures on lamotrigine when compared to placebo treatment. Across all nine crossover studies, lamotrigine produced at least a 50% reduction in partial seizure frequency in approximately 23% of the subjects [Binnie, 1989; Boas, 1996; Jawad, 1989; Loiseau, 1990; Messenheimer, 1994; Sander, 1990; Schapel, 1993; Schmidt, 1993; Smith, 1993]. In the parallel design study, the median partial seizure frequency decreased by 8% in the placebo group, 20% in the 300mg/day lamotrigine group (n.s.) and 36% in the 500mg/day lamotrigine group (p=0.007) [Matsuo, 1993]. Because lamotrigine IR must be given twice daily in the majority of patients, the availability of a formulation given once daily would be desirable. Therefore, GlaxoSmithKline (GSK) set out to conduct a clinical development program to develop lamotrigine XR.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Abstracted from Executive Summary of Primary CMC Review by Dr. Wendy Wilson

"CMC Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approved. The sponsor demonstrated the capacity to manufacture drug product with adequate quality and stability. We agree with the finished drug product specifications at release as well as on stability. The commercial packaging presentations are blister packs and 30-count, 60 cc HDPE bottles with orange, child-resistant, (b) (4) closures. The recommended storage condition is 25°C with excursion permitted between 15 C – 30°C. We concur with the proposed 18 month expiration for the 25 mg strength

tablets packaged in blisters and the 24 month expiration for the 25 mg strength tablets packaged in HDPE bottles. We also concur with the proposed 36 month expiration for the 50, 100, and 200 mg strength tablets packaged in both blisters and HDPE bottles. Based on the sponsor's acceptance of the OCPB-recommended changes to the dissolution specifications, the drug product specifications may need to be updated."

3.2 Animal Pharmacology/Toxicology

There is no information to review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The original, electronic NDA submission files are located in the following directory : \\cdsesub1\n22115\N_000\2006-11-22.

Subsequent sponsor submissions for NDA 21115 were sent to the same location (\\cdsesub1\n22115\N_000\) and assigned a new date, based upon the date of receipt to the Agency.

4.2 Tables of Clinical Studies

Tabular Listing of All Clinical Studies

Table 1 Tabular Listing of All Clinical Efficacy and/or Safety Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
LAM100034	Efficacy and safety	DB, R, PC, PG	Patients with partial seizures	Lamictal extended-release tablets (25, 50, 100 and 200 mg), qd, oral, adjunctive therapy, 100-600 mg/day dependent on concurrent AEDs, 19 weeks for DB phase	243 randomized	DB:Completed (CSR) Continuation: Ongoing
LEP103944	Characterize the pk profile of lamotrigine during conversion from the immediate to extended release formulation (& vice versa)	OL	Patients with epilepsy	Lamictal immediate-release tablets (25, 50, 100 and 200 mg), bid, oral, adjunctive therapy, 2 weeks before and 1 week after Lamictal extended-release Lamictal extended-release tablets, qd, oral, adjunctive therapy, 2 weeks	44 enrolled	Completed (CSR)
Efficacy and Safety Studies: Other Study Reports						

AC = Active control
CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DB = Double-blind
DD = Double dummy
EC-MR = Enteric Coated modified Release
IR = Immediate Release
IV = Intravenous
NR = Non-randomized
OL = Open label
PC = Placebo-controlled
PG = Parallel Group
PGx = Pharmacogenetics
R = Randomized
RD = Rising Dose
SB = Single-blind
SR = Slow Release
UC = Uncontrolled
XO = Crossover

Table 2 Tabular Listing of Clinical Pharmacology Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report)
Pharmacokinetic Studies						
LAM10005	To determine the pharmacokinetic characteristics of the lamotrigine EC modified release prototype tablet formulation on the basis of single dose pharmacokinetic behaviour of the 25 mg at different release rates, and of the 200mg strength at a single release rate.	OL, R, XO	Healthy Subjects	Part A comprised 5 treatment options. Each subject received an oral dose of the reference treatment A and C and one of the three other treatments (B, D or E) with at least 14 day intervals between dosing. A = Lamictal IR 25mg, B = 25mg EC-MR (fast release 12 hrs) no food interaction; C = 25mg EC-MR (slow release 15 hrs) no food interaction, D = 25mg EC-MR (slow 15 hrs) no food interaction, 25mg EC-MR (slow 15 hrs) with food interaction, E = 200mg EC-MR (slow 15 hrs) no food interaction Part B (based on results of Part A) comprised Period 1 single dose of 25mg EC-MR (slow release rate 15 hrs); and in Period 2 following 14 days wash out period they received repeat doses of 25mg EC-MR (fast release rate 12 hrs.) once a day for 14 days.	44	Completed (CPSR)
LAM10005	To determine the pharmacokinetic characteristics of the lamotrigine EC modified release prototype tablet formulation on the basis of single dose pharmacokinetic behaviour of the 25 mg at different release rates, and of the 200mg strength at a single release rate.	OL, R, XO	Healthy Subjects	Part A comprised 5 treatment options. Each subject received an oral dose of the reference treatment A and C and one of the three other treatments (B, D or E) with at least 14 day intervals between dosing. A = Lamictal IR 25mg, B = 25mg EC-MR (fast release 12 hrs) no food interaction; C = 25mg EC-MR (slow release 15 hrs) no food interaction, D = 25mg EC-MR (slow 15 hrs) no food interaction, 25mg EC-MR (slow 15 hrs) with food interaction, E = 200mg EC-MR (slow 15 hrs) no food interaction Part B (based on results of Part A) comprised Period 1 single dose of 25mg EC-MR (slow release rate 15 hrs); and in Period 2 following 14 days wash out period they received repeat doses of 25mg EC-MR (fast release rate 12 hrs.) once a day for 14 days.	44	Completed (CPSR)
LAM10007	To evaluate the relative bioavailability of two formulations (powder and solution) of lamotrigine from three sites in the GI tract compared to reference	OL, R	Healthy Subjects	Four dosing sessions with 14 days between doses. Each volunteer received the reference formulation (Formulation F: 50mg of lamotrigine administered as two immediate release tablets) and three (out of a possible five) test formulations. The test formulation were: A 50mg of lamotrigine powder delivered to the proximal small bowel, B 50mg of lamotrigine powder delivered to the distal small bowel, C 50mg of lamotrigine solution delivered to the distal small bowel, D 50mg of lamotrigine powder delivered to the ascending colon, E 50mg of lamotrigine solution delivered to the ascending colon PK samples were taken up to 120 hours post dose.	15	Completed (CPSR)
LAM10014	Food effect on pharmacokinetics of subjects taking 200mg lamotigine EC modified release tablets	OL, R, PG	Healthy Subjects	Two groups of subjects received a single oral dose. Group A received 200mg tablet of lamotrigine EC modified release formulation under fasted conditions. Group B received 200 mg tablet 10 minutes after completing FDA standard breakfast. PK samples up to 144 hours. Total of 10 days in the study.	95	Completed (CPSR)

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CSR = Clinical Study Report
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DD = Double dummy
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IR = Immediate Release
IV = Intravenous
NR = Non-randomized
OL = Open label
PC = Placebo-controlled
PG = Parallel Group
PGx = Pharmacogenetics
R = Randomized
RD = Rising Dose
SB = Single-blind
SR = Slow Release
UC = Uncontrolled
XO = Crossover

Table 2 (Continued) Tabular Listing of Clinical Pharmacology Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report)
Pharmacokinetic Studies						
LAM10017	To characterise the pharmacokinetic profile of lamotrigine when administered as repeated oral doses of the EC-MR, and IR tablet formulation at daily doses of 25, 50, 100 and 200 mg	OL, R, PG	Healthy Subjects	Subjects randomized into two groups - Lamotrigine IR (group A): IR lamotrigine titrated from a starting dose of 25 mg once a day to a final dose of 100 mg twice daily, using a standard lamotrigine titration schedule. Lamotrigine EC-MR (group B): EC-MR lamotrigine titrated from a starting dose of 25 mg once a day to a final dose of 200 mg once a day, using an equivalent titration schedule. Treatment was for 75 days	60	Completed (CPSR)
LAM102611	To estimate the effect of repeated oral doses of 40 mg esomeprazole on the pharmacokinetics of a single oral dose of 200 mg lamotrigine EC-MR in healthy volunteers	SB, R, PC, PG	Healthy Subjects	Subjects randomised to one of 2 parallel groups to receive a single oral dose of either esomeprazole or placebo once daily for 12 days. On Day 7, all subjects in both groups received one dose of 200 mg lamotrigine EC-MR.	61	Completed (CPSR)
LAM30055	Efficacy and safety	DB, R, PG, Historic control	Patients with partial seizures	Lamictal extended-release tablets (25, 50, 100 and 200 mg), qd, oral, adjunctive therapy (10-11 weeks) withdrawing to monotherapy (250 or 300 mg/day, 12 weeks)	Projection: enroll 230 to randomize 164	Study is ongoing
LAM100036	Efficacy and safety	DB, R, PC, PG	Patients with primary generalized tonic-clonic seizures	Lamictal extended-release (25, 50 100 and 200 mg), qd, oral, adjunctive therapy, 100-600 mg/day dependent on concurrent AEDs, 19 weeks for DB phase	Projection: enroll 216 to randomize 140	Study is ongoing

AC = Active control
CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DB = Double-blind
DD = Double dummy
EC-MR = Enteric Coated modified Release
IR = Immediate Release
IV = Intravenous
NR = Non-randomized
OL = Open label
PC = Placebo-controlled
PG = Parallel Group
PGx = Pharmacogenetics
R = Randomized
RD = Rising Dose
SB = Single-blind
SR = Slow Release
UC = Uncontrolled
XO = Crossover

Table 3 Tabular Listing of Special Clinical Pharmacology (Pharmacodynamic/Pharmacokinetic) "Thorough" QTc Study

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report)
Pharmacokinetic Studies						
SCA104648	To estimate the effect of steady state oral dosing of lamotrigine and single dose moxifloxacin on QTc interval on each active regimen relative to placebo	SB & DB, R, PC, PG	Healthy Subjects	There were 5 dosing sessions. In sessions 1 and 2 (SB) subjects received a single oral dose of 400mg moxifloxacin or placebo on day 1. Subjects were randomly assigned to one of 4 treatment sequences. 7 days later they were crossed over at session 2, so that those given moxifloxacin in session 1 were given placebo and vice versa. Sessions 3, 4 & 5 (DB) commenced after another 7 days. In Group 1 subjects received increasing oral doses of lamotrigine increasing doses of lamotrigine in 3 sessions (25mg, 50mg, 100mg, 200mg, 300mg, 400mg) to Day 77. Group 2 received oral placebo on same days. Subjects were then down-titrated from Day 78-85.	152	Completed (not reported)

4.3 Review Strategy

My review strategy included assessment of : 1) relevant NDA 22115 (for XR lamotrigine) submissions (focusing mostly on randomized, double-blind, placebo-controlled study LAM100034, and also considerably on the IR to XR lamotrigine "conversion" study

LEP103944)) by the sponsor; 2) additional analyses (that I requested from the sponsor); and 3) information (e.g. reviews) from other colleagues (e.g. primary reviewers for CMC, Clinical Pharmacology, Statistics,, consult to QTc Review Team).

4.4 Data Quality and Integrity

The data had appeared to be of reasonable quality. Results from DSI inspections (2 sites in Seoul, Korea) have not yet been received as of 9/14/07.

However, shortly prior to the PDUFA action date, on 9/14/0 I received a sponsor communication (9/10/07 cover letter) noting that its internal, quality control inspection of the 2 Korean sites scheduled for DSI inspection had identified several, various errors (including errors related to seizure rate efficacy data) in transcribing information from source documents to CRFs at both Korean sites.

The following information was communicated to the DNP in this 9/10/07 cover letter.

September 10, 2007

GlaxoSmithKline

Russell G. Katz, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

GlaxoSmithKline
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Re: NDA 022115; LAMICTAL® XR™ (lamotrigine) Extended-Release Tablets
Amendment to Pending Application
General Correspondence: Other

Dear Dr. Katz:

Reference is made to the aforementioned New Drug application, submitted to the Agency on November 22, 2006.

As part of GlaxoSmithKline's (GSK) quality control activities, we conducted an internal review of two clinical sites who participated in LAM100034, the pivotal study submitted with this application. The principal investigators for these sites were Sang-Kun Lee (South Korea) and Sang-Ahm Lee (South Korea). Total enrollment at each site is 10 subjects for Sang-Kun Lee and 16 subjects for Sang-Ahm Lee.

GSK found errors in transcribing information from the source documents to the CRFs at both sites. These errors fall into the following general categories:

- Seizure data: Errors in transcription from seizure diaries to CRFs were noted for nine subjects across both sites. Errors occurred when recording dates and/or the number of seizures for a particular date. In general, the differences in seizure counts were small; however, for one subject, 78 additional baseline seizures were noted. (Also for subject 1817, two fewer seizures were noted at baseline and five fewer seizures during escalation.) In addition, we were notified the 4-5 days of seizure data were unknown for a particular subject as the subject did not return his seizure diary.
- Pharmacokinetic data: errors in transcription of pharmacokinetic data were noted for two subjects randomized to LTG-XR. One error resulted in a slight change in the sample time. These errors would not affect the overall results.

- Investigational product dosing: errors in transcription of dosing information were reported in three patients. One subject received PBO, one error was noted in the taper medication, and the third involved the modal dose change from 400 to 500 mg/day. These errors are not expected to change the overall results.
- Investigational product compliance: Errors in transcription of compliance information was noted for one patient. Previously, the site reported that this subject missed 0 doses of study drug. However, the subject did not take all or part of a dose of study drug on 38 out of 82 days of dosing resulting in estimated compliance of 54%.
- The reason for withdrawal for one patient was changed from "Other" to "Consent Withdrawn"
- Additional non-serious AEs were noted for 5 patients as follows (verbatim terms): cold (2 subjects), diplopia (1 subject), dizziness (1 subject), gastric disturbance (1 subject), fatty liver (1 subject), GB polyp (1 subject), itching (1 subject), somnolence (1 subject), dyspnea (1 subject) and ophthalmitis (1 subject).
- An additional SAE, worsening of seizures, was noted for one patient (Subject 1845), a baseline failure, during their participation in the Open-Label Continuation Phase. A narrative for this subject is provided.

We have also recently discovered an incorrect edit check that queried sites to move any partial or unclassified seizure from the innumerable seizure activity (ISA) CRF page to the countable seizure CRF page. This erroneous edit check affected three subjects in the Double-Blind Phase. We are in the process of re-querying the sites to determine whether the seizures should be categorized as ISA or countable partial seizures.

Based on the errors noted with the seizure count and ISA data, GSK is correcting the database and will reconduct the analysis on the primary efficacy endpoint for LAM100034.

This submission is being provided electronically. Please refer to the attached Guide to Reviewer for details regarding this electronic submission.

If you have any questions regarding this submission, please contact me by telephone at 919-483-6466 or by secure e-mail at betty.a.mcconnell@gsk.com.

Sincerely,

Elizabeth McConnell

Elizabeth A. McConnell, Pharm.D.
Associate Director, Neurology
US Regulatory Affairs

4.5 Compliance with Good Clinical Practices

The sponsor noted that it had following Good Clinical Practices in conducting its clinical studies.

4.6 Financial Disclosures

The following information was abstracted from the sponsor's presentation about financial disclosures related to this sNDA.

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 *FR* 5233), as subsequently revised by publication on December 31, 1998 (63 *FR* 72171) (hereafter collectively referred to as the "rule"),

financial interest information is provided for clinical investigators participating in studies covered by the rule included in this New Drug Application for NDA 22-115; LAMICTAL® (lamotrigine) XR Extended-Release Tablets indicated for adjunctive therapy of partial seizures with or without secondary generalization in patients ≥13 years of age. This statement describes the methods used for the collection and reporting of the investigator financial disclosure information. The original copy of Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and supporting tables, can be found in Module 1 (electronic archive folder "other" and paper archive volume 1).

The following are the "covered clinical studies" for purposes of the rule :

Protocol No.	Protocol Title	Overall Study Start Date	Overall Study Completion Date
LAM10014	An open-label study to demonstrate lack of effect of food on the pharmacokinetics of 200mg lamotrigine enteric-coated modified release tablets in healthy male and female volunteers	16SEP2004	01DEC2004
LAM10017	An open-label study in healthy volunteers to evaluate the repeat dose pharmacokinetics, dose strength equivalence, dose proportionality, safety and tolerability of lamotrigine enteric coated modified release tablets and its relative bioavailability to lamotrigine immediate release tablets	13MAY2005	08NOV2005
LAM100034	A Multicenter, Double-Blind, Randomized, Parallel-group Evaluation of LAMICTAL Extended-release Adjunctive Therapy in Subjects with Partial Seizures	15OCT2004	26JUN2006[1]

1. This represents the date of last subject assessment in the Double-blind phase.

Note: To arrive at the above-noted overall study "start" and "completion" dates, GlaxoSmithKline has defined the overall duration of the clinical study as the time period beginning with the date of enrollment of the first patient entered into the clinical study at the first site until the date of the last patient assessment at the last site of a covered clinical study. However, to the extent investigators have provided financial disclosure information via questionnaires, they were asked to do so based on site-specific (or if shorter, their individual) study start and completion dates.

GlaxoSmithKline exercised due diligence in its attempts to obtain financial disclosure information from all principal investigators and subinvestigators. If the information was unable to be collected upon study completion, further attempts were made through a series of phone calls and letters to the investigator.

Compensation potentially affected by the outcome of the covered study [21

CFR 54.4(a)(3)(i), 54.2(a)]

Neither GlaxoSmithKline nor its predecessor organizations compensates clinical investigators in such a way as the total amount could vary with the outcome of the study. This is now formally stated in an organization-wide policy statement. Consequently, there are no disclosures in this category.

Significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4(a)(3)(ii), 54.2(f)]

GlaxoSmithKline relied upon payments of other sorts data provided by the clinical investigators through questionnaires that were completed at the end of the study to determine if the $25,000 threshold was exceeded in the case of any individual clinical investigator. If, according to their written commitment to GlaxoSmithKline, investigators filed reports of updated payment information to account for any material changes in the 1-year period following study completion, these additional reports were relied on as well. There are no disclosures in this category.

Proprietary interest in the tested product (21 CFR 54.4(a)(3)(iii), 54.2(c))

The sponsor noted that it is its policy not to allow the participation of clinical investigators in a clinical study if they, their spouse or dependent children have proprietary interest in the tested product. This is formally stated in an organization-wide policy statement. Consequently, there are no disclosures in this category.

Significant equity interest in the sponsor of the covered study product (21 CFR 54.4(a)(3)(iv), 54.2(b))

GlaxoSmithKline relied upon equity information provided by the investigators through questionnaires to determine if the $50,000 threshold was exceeded in the case of any individual clinical investigator. If, according to their written commitment to GlaxoSmithKline, investigators filed reports of updated equity interest information to account for any material changes in the 1-year period following study completion, these additional reports were relied on as well. There are no disclosures in this category.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The key ADME characteristics of lamotrigine are derived from the immediate release (IR) formulation. The pharmacokinetic (PK) parameters after the administration of XR lamotrigine are summarized in the following question. Absorption from the XR dosage form is slower as compared to the IR dosage form. Median peak concentrations are reached at 10-14 hours post dose from the XR dosage form at about 1-5 hours from the IR dosage form in healthy volunteers. In epilepsy patients, the median time to peak concentration (T_{max}) following administration of

XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone, 9 to 11 hours in patients taking VPA, and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA.

The distribution, metabolism and elimination characteristics are similar to those of the IR dosage form, with the half-life also being similar with the two dosage forms. The mean half-life was about 37-44 hours in healthy subjects for the XR and about 38 hours for IR dosage form in a crossover study using the 25 mg strength (according the IR label, the mean half-life of the IR dosage form is 33 hours). The half-life of lamotrigine changes depending on the concomitant AED in patients. Although the sponsor has not characterized the half-life of the XR dosage with concomitant AEDs, it is reasonable to expect them to be similar to the IR dosage form. The single and repeat dose pharmacokinetics of 25 mg lamotrigine extended release tablets were evaluated in LAM10005 using the prototype formulation. The final 25 mg tablet remained relatively unchanged other than a change in the manufacturing process, hence can be used do describe single and repeat dose pharmacokinetics.

There was no commercial formulation that evaluated the single dose parameters of all the strengths in a Clinical Pharmacology study. Multiple dose pharmacokinetic parameters of all the strengths of the commercial formulation were evaluated in Study LAM 10017. The single and multiple dose pharmacokinetic parameters from these studies are shown in Table 4.

Table 4 Summary Table of Lamotrigine Pharmacokinetics following Single and Repeat Dose (od) of 25 mg Lamotrigine Extended Release (Geometric mean (CVb%)) [Study LAM10005 using prototype formulation]

Parameter	Single Dose (Day 1)	Repeat Dose (Day 14)
AUC(0-∞) (ug·h/mL)	18.1 (41.7%)	N/A
AUC(0-24) (ug·h/mL)	3.74 (24.8%)	14.3 (38.8%)
Cmax (ug/mL)	0.24 (23.1%)	0.67 (36.4%)
tmax[a] (h)	20.0 (10.0, 24.0)	10.0 (3.98, 20.0)
t1/2 (h)	44.1 (39.5%)	39.4 (37.9%)
Fluctuation Index[b]	Not analysed	0.22 (32.6%)

[a] Median (Range)
[b]Fluctuation Index: (Cmax-Cmin)/Cavg
NA – not applicable to report repeat dose AUC(0-inf)

Based on Study LAM 10005 using the 25 mg strength, there was an approximate 3-fold increase in Cmax and AUC(0-24) following repeat dose administration of the 25 mg XR formulation in comparison to single dose. There was evidence of auto-induction as mean terminal phase half-life decreased from 44 h for a single dose to 39.4 h following repeat dosing. This finding is consistent with that observed with lamotrigine IR. The median time to Cmax (tmax) following repeat dosing of lamotrigine XR was 10 h compared to a median tmax of 20 h for a single dose.

The within-subject variability of steady-state Cmax and AUC in healthy volunteers was (18-20 %, LAM10017). Between-subject variability following both single and repeat dose for Cmax and

AUC in healthy volunteers was ~17-40 %. However, in study LEP 103944 (IR to ER conversion study), between subject variability appeared to be higher (~40-100%). The IR arm in this study also appeared to have high variability. Otherwise in general the variability of 17-40% seen with the XR formulation was consistent with that observed for the IR formulation in previous studies.

The increase in systemic exposure to lamotrigine was dose proportional between 50 and 200 mg XR. At doses between 25 mg and 50 mg, the increase in exposure was less than dose proportional, with a 2-fold increase in dose resulting in an approximate 1.6-fold increase in exposure. This observation is not likely to be considered of any significant clinical relevance as the doses are titrated up starting with 25 mg QD.

Assessment of dose proportionality of the dose range 50-200 mg XR lamotrigine showed dose proportionality for both Cmax and AUC(0-24)ss (Table 5). The slope of the power model was close to unity and the 90% CI was completely contained within the pre-defined range of 0.8391-1.1609.

Table 5 Repeat Dose Pharmacokinetics of Lamotrigine Following Administration of Lamotrigine XR (25, 50, 100 and 200 mg) (Geometric Mean (CVb%) [Study LAM10017 using commercial formulation]

Treatment	N	AUC(0-τ)ss (ug.h/ml)	Cmax (ug/ml)	Tmax (h)	Cτ (ug/ml)	Fluctuation Index
25 mg XR	21	14.5 (24.6)	0.67 (24.3)	14.0 (3-23.9)	0.59 (24.6)	0.13 (0.05-0.20)
50 mg XR	20	23.5 (31.5)	1.08 (31.0)	14.0 (0-23.9)	0.94 (39.4)	0.095 (0.02-0.20)
100 mg XR	19	52.1 (26.9)	2.56 (25.7)	12.0 (0-23.9)	1.93 (31.0)	0.29 (0.07-0.66)
200 mg XR	18	87.4 (26.2)	4.22 (26.9)	10.0 (0.5-23.9)	3.36 (27.3)	0.22 (0.12-0.44)

5.2 Pharmacodynamics

The pharmacodynamic actions of lamotrigine are well known and are described in the label.

Reviewer Comment

- In the Reviewer Comment part (toward the end of the whole section 6.1.4 for Efficacy Findings) of section 6.1.4, I have presented data - Table 30 - that suggest that the efficacy of lamotrigine in terms of anti-seizure effects is not maximal soon after achieving PK steady state but instead seems to increase progressively during prolonged treatment even after achieving PK steady date.

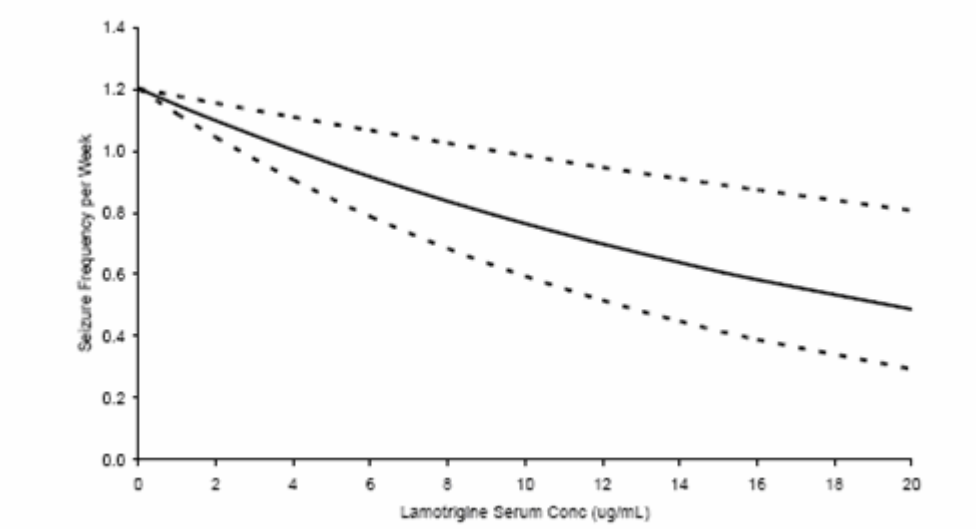
5.3 Exposure-Response Relationships

Exposure response analysis on the extended release formulation was conducted on the pivotal clinical efficacy study (LAM100034 (sparse samples) and the supportive conversion study

LEP104944 (intense sampling), using non-linear mixed effects modeling and accounted for a placebo/time effect, baseline and study effects as well as the lamotrigine concentration. Due to the different study design of the two studies, the percentage change in seizure frequency was available only in study LAM100034, therefore the primary analysis of exposure-response relationships used the seizure frequency rather than its change from baseline.

This modeled analysis suggested that at the end of the study there was a decrease in seizure frequency with increasing lamotrigine concentration (Figure 1). The concentration effect relationship was not affected by the age or sex of the patient, nor was it affected by the concomitant AED therapy.
It should be noted that the relationship between lamotrigine systemic exposure and seizure frequency has not yet been fully evaluated during the clinical development of the immediate release (IR) formulation of lamotrigine.

Figure 1 Exposure-Response Model Predicting Relationship Between Seizure Frequency at End of Study vs Plasma Lamotrigine Concentration (mean, 90 % CI) for Combined Data from Open-Label Study LEP103944 and Double-Blind Placebo-Controlled Study LAM100034

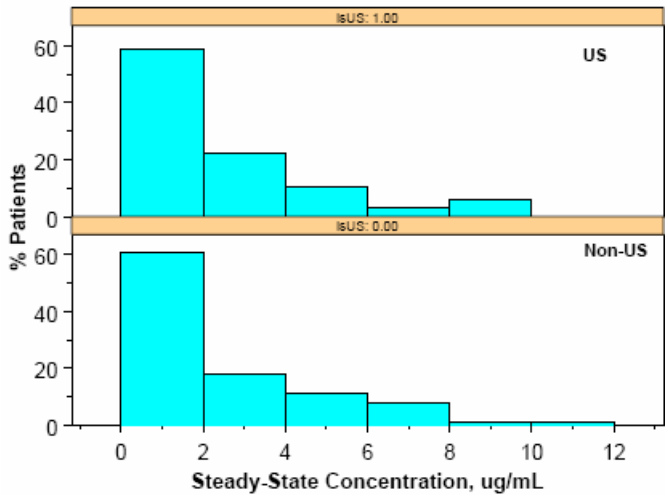


The pivotal trial LAM100034 was conducted at multiple sites around the world (including ~ 40 % of patients in the U.S.). Numerous statistical analyses indicated that the XR lamotrigine treatment effect is markedly diminished in the U.S. patients compared to non-U.S. patients (numerous analyses are presented and discussed toward the end of section 6.1.4 for Efficacy Findings under Reviewer Comment). I advised our Clinical Pharmacology colleagues about this discrepancy and my concern on this issue and asked them about possibly considering additional pharmacokinetic- pharmacodynamic (PK-PD) analyses for the primary analysis of the primary efficacy endpoint for controlled study 34 alone along with plasma lamotrigine levels collected in these same patients for U.S. patients vs non-U.S. patients.

Our Clinical Pharmacology colleagues did not conduct the desired additional exposure-response analyses for the primary efficacy endpoint for U.S vs non-U.S. patients. However, instead of the desired analysis, an additional analysis of a secondary, responder efficacy outcome was assessed relative to 2 categories for lamotrigine levels in U.S. patients vs ALL patients (including U.S. patents with non-U.S. patients.

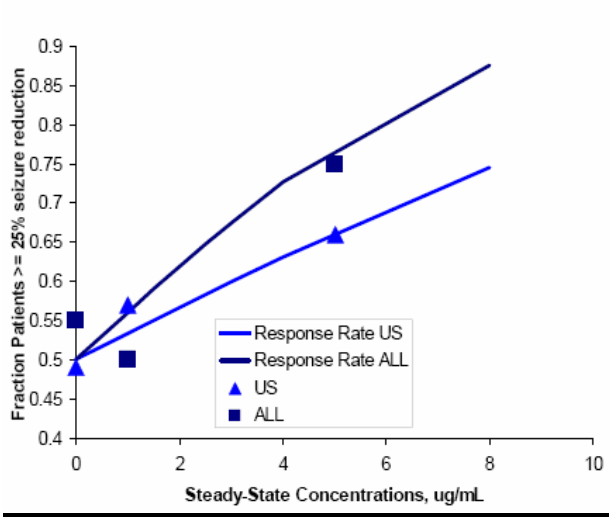
Figure 2 shows the distribution of the average steady-state concentration between U.S. (upper panel) and Non-U.S. (lower panel) sites/patients. The concentrations in U.S. and non-U.S. patients are similar and overlapping.

Figure 2 Distribution of Plasma Lamotrigine Levels for U.S. vs non-U.S. Sites/Patients in Study 34



Lamotrigine steady-state average concentrations were analyzed relative to response rate (e.g. $\geq$ 25% reduction in seizures from baseline; a pre-specified secondary endpoint) for U.S. vs non-U.S. data for the entire treatment duration (double-blind phase). Figure 3 shows results of this additional analysis conducted by our Clinical Pharmacology colleagues. The following quoted section is abstracted from the Clinical Pharmacology review. "The graph below shows a clear exposure-response for both US (N=65) and all (both US and Non US) (N=192) patients. The slope of the concentration response rate curve is significant for both populations (US=0.0493; all=0.029). We did not conduct analysis of non-US alone as non-US included geographically varied sites (Russian Federation, India, Korea). Further separation of non-US sites by region will not render interpretable results due to small sample sizes per site."

Figure 3 **Exposure-Response Relationship for Secondary Efficacy Outcome Responder Endpoint Relative to Steady-State Plasma Lamotrigine Concentrations in U.S. vs ALL. Sites/Patients in Study 34**



Reviewer Comment

- I do not find the exposure-response analysis shown in Figure 1 to be an appropriate, nor a helpful, or desirable analysis because it combines not only results from 2 studies but also efficacy results conducted under blinded conditions with results conducted under open-label conditions and it does not include results for the primary efficacy endpoint used in the critical, pivotal study 34.

- Neither do I find the exposure-response analysis shown in Figure 3 to be an appropriate, nor a helpful, or desirable analysis providing any compelling information for several reasons. Again the primary efficacy endpoint (that was the key efficacy endpoint showing marked differences for U.S. vs non-U.S. patients) was not used in the analysis. Instead, a secondary efficacy endpoint was arbitrarily used and this use of a categorical responder does not allow you to use continuous data generated from each patient. Neither did this analysis compare results for U.S. vs non-U.S. data because the comparison for U.S. data was made with ALL data that included U.S. and non-U.S. data. This approach tends to minimize the actual difference between U.S. vs non-U.S. data that was much larger than when one compared the primary efficacy endpoint for U.S. vs non-U.S. data. Incorrect numbers (N=65 for U.S.; N=195 for non-U.S.) are also provided for the number of patients included in this exposure response analysis. The primary efficacy MITT analysis of the DBP of study 34 included only 42 patients from U.S. sites and 116 patients from ALL sites (N=74 from non-U.S. sites) who had been treated with XR lamotrigine. Although these numbers refer to patients, it may be that these number refer to the number of PK samples for lamotrigine in this analysis. It would also be of interest for an exposure-response analysis showing slopes to have the confidence interval of the slopes (not provided). Finally, I would be interested in also seeing analyses using all actual data (e.g. scatterplot analyses) for the primary efficacy endpoint for each patient and for all

steady state lamotrigine concentrations rather than compartmentalized data in which plasma lamotrigine concentration (I believe) were put into to arbitrary categories of "high" or "low" levels and used as 2 bins of PK data.

- I also believe that it would be interesting to compare exposure-response analyses from actual data (analyzed in scatterplots showing R value, slope, slope CI, p-value) with data from modeling approaches using the same data.

- I strongly believe that we should ask the sponsor not only to address the lack of a response for the primary efficacy endpoint for U.S. data but also to conduct additional exposure-response analyses. These analyses (U.S. vs non-U.S. data) should include cumulative efficacy data for the primary efficacy endpoint (change of weekly seizure rate from baseline) at weeks 11, 15, and 19 and the plasma steady state lamotrigine levels collected at these same times.

- In my view, the following comparative, exposure-response analyses (U.S. vs non-U.S. data) would be desirable (at a minimum) separately as scatterplot analyses and as modeled analyses using all data in each group and only "paired data" (i.e. some or all PK when the corresponding efficacy data are also available in each patient) .

    - Response = All efficacy data for cumulative % partial seizure rate change from baseline for all patients at weeks 11, 15, and 19 (or end of study - EOS for premature discontinuations – D/C) (Y-axis) vs
      Exposure = All plasma lamotrigine levels (X-axis) at weeks 11, 15, and/or 19 (or EOS for premature D/C)

    - Response = Efficacy data for cumulative % seizure rate change from baseline at weeks 11, 15, and 19 (or EOS for premature D/C) **ONLY** when "paired" PK data (see above description of term "paired") are available (Y-axis) vs
      Exposure = All patients (X-axis) who also have corresponding "paired" plasma lamotrigine levels at weeks 11, 15, and 19 (or EOS for premature discontinuations) at the respective cumulative efficacy timepoint

    - Response = All efficacy data for cumulative % seizure rate change from baseline at week 19 (or EOS for premature D/C) for all patients (Y-axis) vs
      Exposure = All plasma lamotrigine levels (X-axis) at week 19 (or EOS for premature D/C)

    - Response = Efficacy data for cumulative % seizure rate change from baseline at week 19 (or EOS for premature D/C) **ONLY** when "paired" PK data (see above description of term "paired") are available (Y-axis) vs
      Exposure = All plasma lamotrigine levels (X-axis) at week 19 (or EOS for premature D/C)

- Response = Efficacy data for cumulative % seizure rate change from baseline for all patients at week 19 (or EOS for premature D/C) (Y-axis) vs
  Exposure = Mean of all plasma lamotrigine levels (X-axis) at weeks 11, 15,and 19 (or EOS for premature D/C)

- Response = Efficacy data for cumulative % seizure rate change from baseline at week 19 (or EOS for premature D/C) **ONLY** when "paired" PK data (see above description of term "paired") are available at 2 or 3 timepoints (from week 11, 15, 19 planned PK samplings) (Y-axis) vs
  Exposure = Mean of all plasma lamotrigine levels (X-axis) at weeks 11, 15, and 19 (or EOS for premature D/C)

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

A single randomized, double-blind, placebo-controlled study (LAM100034) was submitted to demonstrate efficacy for LTG XR.

The following information outlines the sponsor's planned statistical analysis that was included in the study protocol. No interim analysis was planned and the sponsor specifically informed us that none conducted

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

Other Comparisons of Interest
Comparisons of LTG and PBO were made using a two-sided level of significance for each secondary endpoint. The ITT and Per Protocol efficacy populations were to be used for all secondary comparisons.

Sample Size Considerations/Assumptions
The primary endpoint was to be percent change in partial seizure frequency between the Baseline and Double-Blind Treatment Phase. Assuming an estimated pooled standard deviation of 3.5 seizures per week and a baseline rate of 4 seizures/week, 132 randomized

subjects were planned to provide 90% power to detect a 50% difference between treatment groups at a two-sided 5% alpha level based on a t-test. **Assuming a 35% drop-out rate during the Baseline Phase, approximately 204 subjects were to be enrolled in order to randomize 132 subjects.** Subjects were to be centrally randomized in a 1:1 ratio to receive either lamotrigine or matching placebo.

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

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

Sample Size Re-estimation
No re-estimation of sample size was planned for this study.

Analysis Populations

The following populations were to be considered for analyzing the data :

• Intent-to-Treat (ITT) efficacy population: defined as all subjects who take at least one dose of study drug and have at least one post-baseline efficacy assessment in the Double-blind Treatment Phase.

• Per Protocol efficacy population: defined as of all subjects who complete the double-blind treatment phase, excluding those with major protocol violations.

• Safety Population: defined as all subjects who take at least one dose of the study drug.

Data Sets
With the exception of the weight endpoint, an observed data set was to be used to analyze all efficacy and safety endpoints. An LOCF data set was to be used for the analysis of weight data.

Missing Data
Seizures that are impossible to count, as noted on the innumerable seizure activity CRF page, "Innumerable Seizure Activity and Status Epilepticus") were to be imputed. The highest daily seizure count observed during a given phase (Baseline, Escalation, Maintenance) was to be used as the seizure count on these days.

For the change from baseline to end of study weight analysis only, LOCF was to 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 was to be assigned to the missing weight value. Screening values were not planned to be carried forward.

Derived and Transformed Data

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

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

Multiple Comparison Strategy

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

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

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

Time to ≥ 50% reduction in Seizure Frequency

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

Change from Baseline to Endpoint in Weight

The change from baseline to endpoint in weight was to be tested only if the primary endpoint is significant at the 0.05 level of significance. A Confidence Interval (CI)

approach will be used to evaluate the significance of the change from baseline in weight.

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

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

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

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

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

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

Analysis Plans

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

randomized/treated patients with any primary efficacy endpoint data) and Per Protocol efficacy populations.

Seizure Frequency
The percent change from Baseline in weekly partial seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase will be analyzed using the Wilcoxon Rank Sum test.

The proportion of subjects with ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in weekly partial seizure frequency during the entire Double-Blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase will be analyzed using a Fisher's exact test.
Time to ≥ 50% reduction in seizure frequency
Time to ≥ 50% reduction in seizure frequency will be analyzed using a two-sided logrank statistic. Kaplan-Meier methodology will be used to estimate and graph the time to 50% reduction curve for each treatment group.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was the median percent change from Baseline in average weekly partial seizure frequency during the entire Double-Blind Treatment Phase. This is a standard, frequently used primary efficacy endpoint in epilepsy trials seeking to demonstrate efficacy of an anticonvulsant, especially in trials for adjunctive treatment of partial epilepsy.

Other secondary efficacy endpoints included :

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

6.1.3 Study Design

This was an international, multicenter, double-blind, randomized, parallel-group evaluation of LTG XR adjunctive therapy in subjects with partial seizures. The study consisted of 2 phases, a randomized, double-blind, placebo-controlled study phase (DBP), and an open-label continuation/extension phase (OLP) as DBP and OLP.

The time and events schedule is provided in Table 4. Study phase is depicted in Figure 4 and Table 7 shows the outline for the duration of each study phase.

Figure 4 Schematic of Study Design for DBP and OLP of Study LAM100034

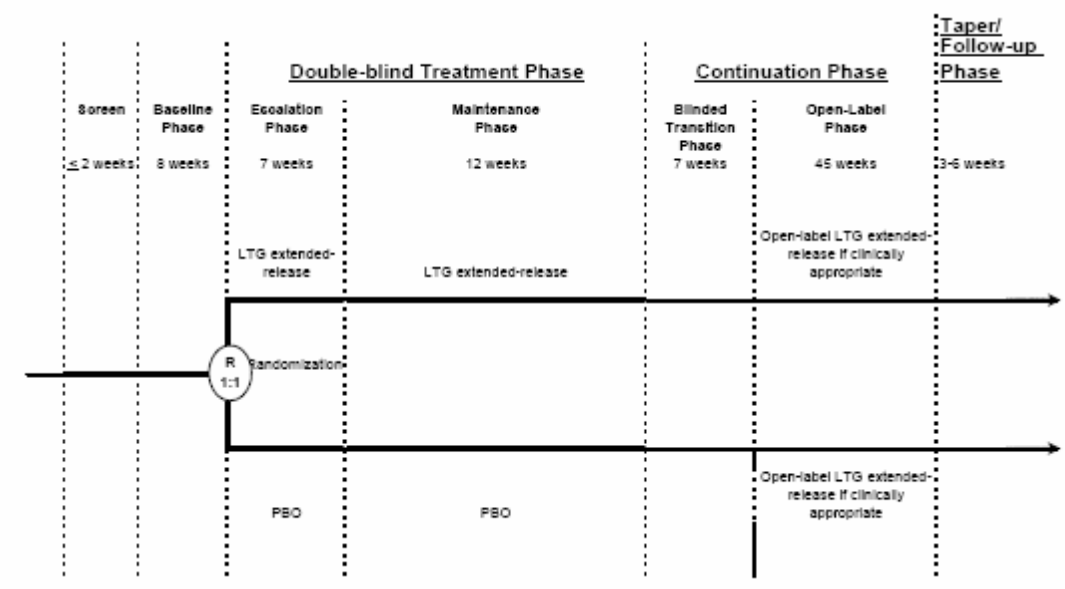


Table 6 Time and Events Schedule

Event	Screen	Baseline Phase		Double-blind Treatment Phase					Continuation Phase[1,2]						Taper/ Follow-up Phase[3]
				Escalation		Maintenance			Transition		Open-label				F/U visit
Visits	V1	V2	V3	V4	V5	V6	V7	V8[5]	V9	V10	V11	V12	V13	V14	V15
Week (i.e., end of specified week)	≤2 Wks	Base Wk 4	Base Wk 8	Treat Wk 3	Treat Wk 7	Treat Wk 11	Treat Wk 15	Treat Wk 19 /End	Con Wk 3	Con Wk 7	Con Wk 19	Con Wk 31	Con Wk 43	Con Wk 52 /End	3 wks after last dose
Eligibility															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demography	x														
Safety															
Vital Signs	X----------X														
Body weight/height	X			X		X		X							
Medical & Seizure history	X														
Physical Exam	X							X							
Full Neurological Exam	X							X							
Brief Neurological Exam				X		X									
Urine Pregnancy Test[6,7]	X		X	X		X		X							X
Hematology/Clin Chemistry	X			X		X		X							
Adverse Events		X----------X							X----------X						
ECGs and Urinalysis	X							X							
Treatment															
Study Drug Dispensing, accountability & Compliance			X----------X						X----------X						
Concurrent AEDs/Compliance & Concurrent Medications	X----------X								X----------X						
Efficacy															
Seizure Counts	X----------X								X----------X						
Investigator's Assessment of Clinical Status and Subject's Satisfaction Questionnaires	X														
Pharmacokinetics															
LTG Serum levels						X	X	X							
Pharmacogenetics															
Blood samples			X												
Health Outcomes															
Profile of Mood State	X							X							
Center for Epidemiological Studies-Depression Scale	X							X							
Neurological Disorders Depression Inventory-Epilepsy	X							X							
Quality of Life in Epilepsy-31-P	X							X							
Liverpool Adverse Experience Profile	X							X							
Seizure Severity Questionnaire	X							X							
Epworth Sleepiness Scale	X							X							

Continued

1. For randomized subjects: The conversion from study drug to open-label lamotrigine will be conducted in a double-blind fashion during the Transition Phase. During the open-label portion of the Continuation Phase, the investigator will manage the patient according to his/her usual medical practice. Subjects prematurely discontinuing from the Continuation Phase will have an end of Continuation Phase visit and the procedures for the last Continuation Visit (Visit 14) will be performed.
2. For subjects who were not randomized: The Continuation Phase will be 26 weeks in duration. At Continuation Week 26, or at premature discontinuation, the assessments for Visit 14(i.e., the end of Continuation Phase) will be performed. During the open-label portion of the Continuation Phase, the investigator will manage the patient according to his/her usual medical practice.
3. The Taper/Follow-up Phase will last a maximum of 6 weeks for subjects who taper off of study drug and a minimum of 3 weeks for subjects completing/withdrawing from the open-label Continuation Phase who will switch to commercially available LAMICTAL IR.
4. All subjects must have a Follow-up Visit 3 weeks after their last dose of study drug. This includes subjects who are tapering off of study drug treatment and those subjects who are not tapering.
5. Subjects who discontinue the Double-Blind Treatment Phase prematurely will return to the clinic for an end of Double-Blind Treatment Phase visit and will complete the procedures outlined for Treatment Week 19 (Visit 8).
6. For female subjects of child bearing potential.
7. A urine pregnancy test must also be performed three weeks after the subject's last dose of study drug.
8. PGx sample may be taken at any time after the PGx informed consent has been obtained

After completion of all screening procedures, subjects who met the enrollment criteria entered the Baseline Phase for determining baseline seizure frequency. At the end of the 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.

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, if clinically appropriate, for up to 52 weeks.

The maximum duration of the study was approximately 87 weeks (Table 7).

Table 7 Study Phase Duration (LAM100034)

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

The sponsor noted that subjects were randomized 1:1 to placebo or LTG XR to guard against systematic bias. The inclusion/exclusion criteria were similar to previous placebo-controlled LTG IR studies in partial seizures where consistent differences between treatment groups were observed. The major difference was the allowance of up to 4 weeks of historical seizure data at baseline (for subjects who qualified).

Seizure frequency for historical and prospective baseline were examined to determine if reporting differences exist between these groups.

Lamotrigine XR Daily Dosing and Dose Escalation/Titration

Patients were dose according to the scheme (considering concomitant AED class) outlined in Table 8.

Table 8 Lamotrigine XR (Lamictal) Daily Dosing and Escalation/Titration

	ESCALATION					MAINTENANCE
Concurrent Therapy	Treatment Weeks 1-2	Treatment Weeks 3-4	Treatment Week 5	Treatment Week 6	Treatment Week 7	Treatment Weeks 8-19
Subjects taking VPA (with or without another AED)	12.5mg/day (given as 25mg every other day)	25mg/day (once-daily)	50mg/day (once-daily)	100mg/day (once-daily)	150mg/day (once-daily)	Target dose: 200mg/day[a] (once-daily)
Subjects taking an EIAED[d] (with or without another AED other than VPA)	50mg/day (once-daily)	100mg/day (once-daily)	200mg/day (once-daily)	300mg/day (once-daily)	400mg/day (once-daily)	Target dose: 500mg/day[b] (once-daily)
Subjects taking AED(s) other than VPA and EIAEDs[d]	25mg/day (once-daily)	50mg/day (once-daily)	100mg/day (once-daily)	150mg/day (once-daily)	200mg/day (once-daily)	Target dose: 300mg/day[c] (once-daily)

a. If a subject cannot tolerate 200mg/day, the dose can be decreased to a minimum of 150mg/day. If seizure control is inadequate, the dose can be increased to a maximum of 250mg/day.
b. If a subject cannot tolerate 500mg/day, the dose can be decreased to a minimum of 400mg/day. If seizure control is inadequate, the dose can be increased to a maximum of 600mg/day.
c. If a subject cannot tolerate 300mg/day, the dose can be decreased to a minimum of 200mg/day. If seizure control is inadequate, the dose can be increased to a maximum of 400mg/day.
d. For purposes of this study, the major EIAEDs include carbamazepine, phenytoin, phenobarbital and primidone. The major non-inducers are defined as oxcarbazepine, levetiracetam, topiramate, gabapentin, zonisamide and tiagabine.

Summary of Patient Selection Based Upon key Inclusion and Exclusion Criteria

The following are key study **inclusion criteria** :

- male or female subjects ≥13 years of age;
- subjects with a confident diagnosis of epilepsy with partial seizures for more than 24 weeks prior to the Baseline Phase were eligible for entry into the study;
- subjects must have had partial seizures inadequately controlled by a stable regimen of one or two AEDs;
- subjects must have had a documented history of partial seizures, and had to have at least 8 partial seizures (i.e., simple or complex partial seizures with or without secondary generalization) during an 8-week (i.e., 56 days) prospective Baseline Phase with at least one partial seizure occurring during each 4-week (i.e., 28-day) period;
- subjects were to be currently treated with a stable regimen of one or two AED(s) for at least 4 weeks prior to starting the Baseline Phase (historical or prospective).

The following are key study **exclusion criteria**:

- for exhibiting any primary generalized seizures (e.g., absence, myoclonic, PGTC seizures);
- for exhibiting had status epilepticus within the 24 weeks prior to, or during, the Baseline Phase;
- for taking ≥ 3 AEDs chronically;
- if prior or concurrent treatment with lamotrigine, felbamate, or ketogenic diet;
- for abusing alcohol and/or other substance(s);
- for taking an investigational drug within the previous 30 days or planned to take an investigational drug anytime during the study;

- for receiving chronic treatment with any medication that could have influenced seizure control;
- if history of acute or progressive neurological disease, severe psychiatric disease, or a severe mental abnormality that were likely to interfere with the objectives of the study;
- if history of clinically significant cardiac, renal, hepatic condition, or a condition that affected the absorption, distribution, metabolism or excretion of drugs.

The inclusion/exclusion criteria in LAM100034 were similar to previous placebo-controlled lamotrigine IR studies in partial seizures in which consistent differences in favor of lamotrigine IR were observed.

Protocol Amendments

The original protocol, dated 7 June 2004, was amended one time (Amendment 1, dated 18 November 2004) and applied to all sites worldwide. The following outlines and describes key/significant features of this single amendment.

• The dose escalation schedule for female subjects on hormonal contraceptives taking AED(s) other than VPA and EIAEDs was eliminated. These subjects are now treated according to the same dose escalation schedule as all other subjects taking AED(s) other than VPA and EIAEDs. All subjects now have a 7-week Escalation Phase and a 12-week Maintenance Phase;

• Unless approval was given by the GSK medical advisor to enter the Continuation Phase, subjects who prematurely discontinue from the Double-Blind Treatment Phase entered the Taper/Follow-up Phase.

• The Continuation Phase was extended from a total of 31 weeks to a total of 52 weeks for subjects completing the Double-Blind Treatment Phase. The Continuation Phase for subjects who did not meet randomization seizure criteria (i.e., baseline failures) was also extended from a total of 19 to a total of 26 weeks (7 weeks Transition and 19 weeks Open-label.

• Subjects using up to 4 weeks of historical baseline seizure data who did not meet the randomization seizure criteria after completing the prospective Baseline Phase were allowed to enter the Open-label Continuation Phase for 26 weeks.

• The length of time in which missed doses of study drug may have been taken was extended from 4 hours to no later than 12 hours after the scheduled time.

• Oxcarbazepine was considered a non-inducing AED.

• The time period for collecting and recording adverse events (AEs) for baseline failures who entered the open-label Continuation Phase began on the day of the first dose of study drug. Serious adverse events (SAEs) that were related to study participation or to a concurrent medication continued to be collected and recorded from the time the subject consents to participate in the study until he/she was discharged.

• The duration of the study drug taper was 3 weeks instead of 4 weeks.

• It was clarified that innumerable seizure activity did not count toward the number of baseline seizures required for randomization.

6.1.4 Efficacy Findings

Demographic Characteristics

Demographic characteristics are presented in Table 9. The age, sex, and ethnicity distributions were similar between treatment groups.

Table 9 Demographic Characteristics (ITT Population: Study LAM100034)

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

Data Source: Table 6.7, Table 6.8

Baseline Seizure Data

Baseline seizure data are summarized in Table 10. The distribution of seizure types and baseline means (all partials, historical, or prospective) were similar between the two treatment groups.

Table 10 Baseline Seizure Data (ITT Population: Study LAM100034)

Baseline Data	PBO N=120	LTG XR N=116
Baseline Seizure Type[1], n (%)		
A (Simple Partial Seizures)	58 (48)	54 (47)
B (Complex Partial Seizures)	91 (76)	83 (72)
C (Partial Seizures Evolving to Secondarily Generalized Seizures)	42 (35)	38 (33)
D1 (Generalized Seizures, Typical Absence)	1 (<1)	1 (<1)
E (Unclassified Seizures)	2 (2)	0
Both Partial and Generalized Seizures	1 (<1)	1 (<1)
Partial Seizures Only (A, B, or C)	119 (>99)	115 (>99)
Baseline Seizure Frequency per Week (last 8 weeks)- All Partial Seizures		
Entire Baseline, n	120	116
Median (Range)	2.1 (0.9, 50.0)	2.3 (0.5, 59.0)
Historical Baseline, n	41	31
Median (Range)	2.3 (0.9, 33.8)	2.6 (1.0, 18.7)
Mean (SD) Age at First Seizure (yrs)	16.4 (13.73)	14.9 (12.20)
Mean (SD) Duration of Epilepsy (yrs)	22.1 (16.08)	21.8 (13.20)

Data Source: Table 6.10, Table 6.11, Table 6.12

1. Subjects may have been counted more than once.

Concurrent AED Therapy

A summary of the most common (incidence of ≥ 5% of subjects in either treatment group) concurrent AED therapy is presented in Table 11. Concurrent AED therapy was similar between the two treatment groups.

Table 11 Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Concurrent AED Therapy (ITT Population: Study LAM100034)

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

Data Source: Table 6.14

A summary of the number of AED concomitant medications and AED group is provided

In Table 12. The frequency of subjects taking 1 AED was slightly higher in the LTG XR group (51%) compared with the placebo group (41%). Correspondingly, the frequency of subjects taking 2 AEDs was slightly higher in the placebo group (58%) compared with the LTG XR group (49%). There appeared to be a notable difference (in treatment groups) in the % of patients taking VPA with EIAEDs and EIAEDs alone or with "neutral" AEDs that do not alter plasma lamotrigine levels.

Table 12 Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100034)

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

Data Source: Table 6.15

Disposition of Subjects

A summary of the disposition of patients randomized to treatment is provided in Table 13. A greater percentage of subjects in the LTG XR group (20 %) compared with the placebo group (13 %) were prematurely withdrawn from the study and the main reason for this difference appeared to be related to TEAEs.

Table 13 Patient Disposition (All Randomized Subjects: Study LAM100034)

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

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

Maximal XR Lamotrigine Dosing in DBP

Table 14 shows the distribution (across %iles) of maximal, daily XR lamotrigine achieved for all patients (and according ot concomitant AED grouping) in the DBP.

Table 14 Distribution of Maximal XR Lamotrigine Daily Dose (mg/day) for All Patients and According to Concomitant AED Grouping/Class

Concomitant AED Group	Percentile	Dose
Overall	10	200.00
	20	200.00
	30	300.00
	40	300.00
	50	400.00
	60	500.00
	70	500.00
	80	500.00
	90	500.00
	100	600.00
Any VPA	10	200.00
	20	200.00
	30	200.00
	40	200.00
	50	200.00
	60	200.00
	70	200.00
	80	200.00
	90	250.00
	100	600.00
EIAEDs alone or with non-inducing/inhibiting AEDs	10	400.00
	20	500.00
	30	500.00
	40	500.00
	50	500.00
	60	500.00
	70	500.00
	80	500.00
	90	600.00
	100	600.00
All other regimens	10	300.00
	20	300.00
	30	300.00
	40	300.00
	50	300.00
	60	300.00
	70	300.00
	80	300.00
	90	300.00
	100	400.00

Primary Efficacy Results

The primary endpoint was the median percent partial seizure frequency during the entire Double-Blind Treatment Phase. The median percent reduction from Baseline in all partial seizure frequency during the entire Treatment Phase was greater in the LTG XR group (46.1%) than in the placebo group (24.2%; p=0.0004) (Table 15).

Table 15 Primary Analysis of the Median Percent Reduction in Partial Seizure Frequency During the Entire Treatment Phase (ITT Population: Study LAM100034)

All Partial Seizures (A-C)	PBO N=120	LTG XR N=116
n	120	116
Median (Range)	24.2 (-231, 100)	46.1 (-177, 100)
Estimated Difference[1]	18.17	
95% CI for Difference[1]	8.301, 28.025	
p-value[1]	0.0004	

Data Source: Table 7.1, Table 7.2

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

The median percent reduction from Baseline in all partial seizure frequency was greater in the LTG XR group than in the placebo group (median difference: 24.67) during the entire Treatment Phase for the Per-Protocol Population (95% CI between group difference: 13.904, 34.968, p<0.001).

Secondary Efficacy Results (Nominal P values are presented without adjustment for multiplicity)

Seizure Frequency

The median percent reduction from Baseline in average weekly partial seizure frequency during the Escalation Phase, the Maintenance Phase, and the last 8 weeks of Maintenance Phase for the ITT Population is summarized in Table 16. The median percent reduction from Baseline in partial seizure frequency was greater in the LTG XR group than in the placebo group for the Escalation Phase (p=0.0277), the Maintenance Phase (p<0.0001) and the last 8 weeks of Maintenance Phase for the ITT Population (p<0.0001). Statistically significant differences were similarly observed for the Per-Protocol population

Table 16 Analysis of the Percent Reduction in Partial Seizure Frequency During Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT Population: Study LAM100034)

All Partial Seizures (A-C)	PBO N=120	LTG XR N=116
Escalation Phase		
n	120	116
Median (Range)	16.3 (-222, 100)	28.0 (-266, 100)
Estimated Difference[1]	12.70	
95% CI for Difference[1]	1.299, 22.563	
p-value[1]	0.0277	
Maintenance Phase		
n	117	106
Median (Range)	26.7 (-270, 100)	58.0 (-139, 100)
Estimated Difference[1]	28.81	
95% CI for Difference[1]	16.667, 38.310	
p-value[1]	<0.0001	
Last 8 Weeks of Maintenance Phase		
n	117	106
Median (Range)	27.0 (-264, 100)	66.7 (-145, 100)
Estimated Difference[1]	30.00	
95% CI for Difference[1]	17.532, 42.157	
p-value[1]	<0.0001	

Data Source: Table 7.1, Table 7.2

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

The percent reduction from Baseline in partial seizure frequency by discrete categories

(≥ 25%, 50%, 75% and 100% reduction) for the entire Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of Maintenance Phase is presented in Table 17 for the MITT Population.

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

Table 17 Percent Reduction from Baseline in Partial Seizure Frequency (ITT) Population: Study LAM100034)

	PBO N=120 n (%)	LTG XR N=116 n (%)	p value[1]
Entire Treatment Phase			
n	120	116	-
≥25% Reduction	59 (49.2)	78 (67.2)	0.0057
≥50% Reduction	29 (24.2)	49 (42.2)	0.0037
≥75% Reduction	6 (5.0)	20 (17.2)	0.0032
100% Reduction	1 (0.8)	3 (2.6)	0.3634
Escalation Phase			
n	120	116	-
≥25% Reduction	51 (42.5)	61 (52.6)	0.1514
≥50% Reduction	25 (20.8)	32 (27.6)	0.2869
≥75% Reduction	6 (5.0)	14 (12.1)	0.0624
100% Reduction	2 (1.7)	3 (2.6)	0.6796
Maintenance Phase			
n	117	106	-
≥25% Reduction	62 (53.0)	83 (78.3)	<0.001
≥50% Reduction	39 (33.3)	65 (61.3)	<0.001
≥75% Reduction	15 (12.8)	39 (36.8)	<0.001
100% Reduction	6 (5.1)	20 (18.9)	0.0016
Last 8 Weeks of Maintenance Phase			
n	117	106	-
≥25% Reduction	65 (55.6)	83 (78.3)	0.0004
≥50% Reduction	38 (32.5)	68 (64.2)	<0.0001
≥75% Reduction	20 (17.1)	48 (45.3)	<0.0001
100% Reduction	7 (6.0)	21 (19.8)	0.0022

Data Source: Table 7.5

1. p-value using a Fisher's Exact test comparing the number of subjects with the given percent reduction in seizure frequency

Time to Greater than or Equal to 50% Reduction in Seizure Frequency

An analysis of time to ≥ 50% reduction in partial seizure frequency is summarized in Table 18 for the ITT Population. For the ITT Population, time (in weeks) to ≥ 50%

reduction in seizure frequency for the entire Treatment Phase was statistically significant (p=0.0007).

Table 18 Analysis of Time (in Weeks) to 50% Reduction in Seizure Frequency for All Partial Seizures (ITT Population: Study LAM100034)

50% Reduction[1] Up to Time (in Weeks)	Number (%) of Subjects	
	PBO N=120	LTG XR N=116
2	8 (6.7)	15 (12.9)
4	9 (7.5)	23 (19.8)
8	14 (11.7)	33 (28.4)
12	18 (15.0)	39 (33.6)
16	24 (20.0)	45 (38.8)
19	29 (24.2)	49 (42.2)
Treatment Comparison p-value	0.0007	

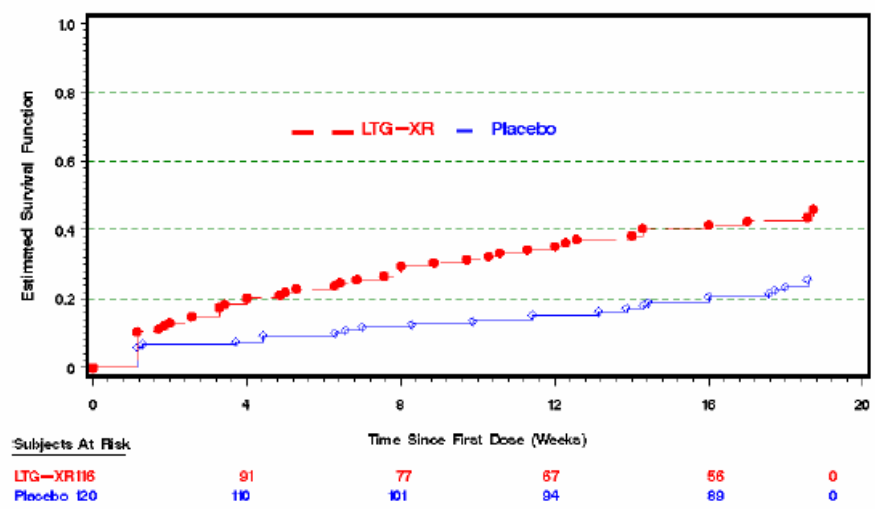
Data Source: Table 7.7

Note: The first eligible time to achieve the endpoint is at Week 1. All observations were censored at the end of Week 19 [Day 133]; Active vs. placebo treatment effect p-values based on log rank test.
The onset of efficacy was seen as early as Day 18 (p=0.0448).

1. 50% reduction in seizure frequency is defined as the time at which a subject first achieved and maintained a ≥50% reduction in seizure frequency following exposure to at least one week of study drug.

The sponsor noted that the treatment difference for this responder outcome reached statistical significance as early as Day 18 of the Escalation Phase (p=0.0448), as shown in Figure 5. A similar result was observed for the Per-Protocol Population (p=0.0004).

Figure 5 Time to 50% Reduction in Seizure Frequency (ITT Population: Study LAM100034)



Note: Statistical Significance was seen as early as Day 18 (p=0.0448).

Source Data: Figure 7.1

Reviewer Comments

- The primary analysis of the primary efficacy endpoint shows that XR lamotrigine is statistically superior to placebo for all randomized patients **(**Table 15).

- The statistical reviewer made an important observation related to the facts that the sponsor over-enrolled (by ~ 52 %) and over-randomized (~ 84 %) more patients than had been planned as per the protocol (see Statistical Review for more details). These increased numbers occurred without a protocol amendment. The protocol had planned to enroll 204 patients in order to obtain 132 randomized patients total based on an assumed baseline dropout rate of 35%. However, a much larger number (N=308) was enrolled and nearly twice as many patients (N=243) were randomized. Dr. Massie, the primary statistical reviewer inquired of the sponsor about these issues and the following sponsor responses to specific questions are shown below in italics.

"Agency Request 1 : Please provide the number of patients that were enrolled.

GSK Response : A total of 329 subjects entered the Screen Phase. Twenty one subjects did not meet the screening criteria, 308 subjects were enrolled into the 8-week baseline phase of which 243 subjects were randomized to the Double-blind Treatment Phase.

Agency Request 2 : Please explain, in writing, why so many more patients were randomized than planned and provide any relevant documentation.

GSK Response : Initially, patient enrollment was slower than projected, therefore, several countries were added later to allow completion of the study enrollment targets.

Since a number of patients had been identified by some of the countries in anticipation of the approval to proceed and since the failure rate during the 8-week baseline phase was unknown for some of the countries which have not previously conducted epilepsy clinical trials with GSK, a decision was made to allow them to continue to enroll patients. Overenrollment was permitted to ensure appropriate number of evaluable patients would be achieved at the end of the 8-week baseline phase. (Bold provided by reviewer for emphasis)

Agency Request 3 : Were there any blinded or unblinded interim looks at the data? Please provide any relevant documentation.

GSK Response : There were no blinded or unblinded interim looks of the data.

Agency Request 4 : Was any sample size re-estimation done?

GSK Response : We did not perform a sample size re-estimation during the conduct of this trial.

Agency Request 5 : Who had access to the data during the trial and were there any limits on the access?

GSK Response : For the purpose of dispensing study medications, the dispensing pharmacists and their back-ups knew the treatment assignment; however, the unblended personnel were not permitted to reveal the treatment assignment to blinded study personnel. Unblinded site staff could not be involved in any other aspect of the study. Study drug, dispensing logs, and treatment assignments were to be kept in a secure location.

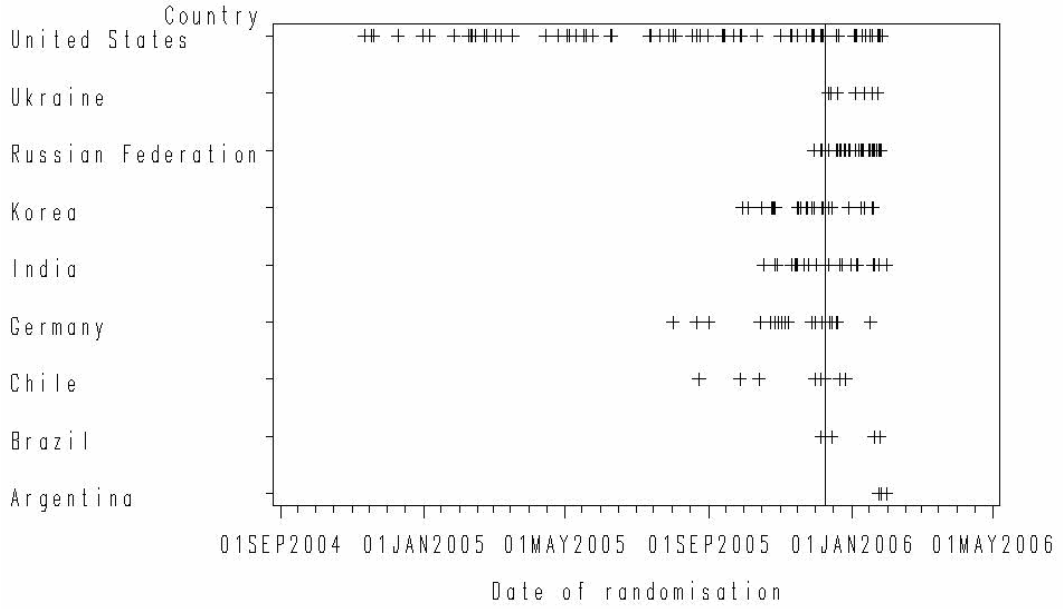
Further, in order to avoid analyzing pharmacokinetic samples from subjects who had received placebo, the protocol permitted release of the randomization code to GSK Worldwide Bioanalysis Department. It was not permitted to communicate this information to anyone outside of this department or the approved bioanalytical contract laboratory prior to database freeze.

Finally, in the event of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject, the investigator was permitted to unblind a subject's treatment assignment by contacting GSK.

Blinding of LAM100034 is discussed further in Section 5.4.4 of the Clinical Study Report provided in the initial application."

- The above sponsor response attempting to explain the marked over-enrollment and over randomization seemed to revolve around the sponsor's potential concern about the completion vs failure rate of the 8 week prospective baseline seizure rate collection in countries with which the sponsor did not have experience for epilepsy studies. An analysis of time of randomization by Dr. Massie showed that full randomization of the first 132 patients (as had been planned) was achieved in 12/05 and that the additional randomization of the excessive 111 patients occurred over approximately the next 2 months (Figure 6).

Figure 6 Date of Randomization for Each Patient by Country



The vertical line shows the time at which the 132nd patient (the planned sample size) was randomized.

Although the sponsor's concern about obtaining a sufficient number of evaluable patients seemed like a legitimate one, it seems that the sponsor still might have been able to cease randomization of such an excessive number of patients if the sponsor monitored site information more closely about completion rate of the prospective baseline period in patients subject to randomization.

- The DNP also entertained concerns about the sponsor's plans for using and actual recruitment of foreign investigation sites (especially outside North America and Europe). Initially, the sponsor planned patient enrollment primarily in the U.S. and a smaller percentage from foreign sites, however, these plans changed quite dramatically over time. In response to a DNP inquiry about this issue the sponsor provided the following information shown below in italics related to site recruitment and dealing with GSK Clinical Operations (CO) in foreign locations. Figure 7, provided by the sponsor shows the chronology of projected vs actual patient enrollment.

"Also in May 2004 the Study Team selected 63 US sites. In June 2004 10 more sites US sites were added. The site status was as follows: US to contribute 73 sites, Argentina 3 sites, Brazil 2 sites, Chile 3 sites, and India 6 sites. The patient allocation was projected to be approximately 70% from the US and 30% from International countries. It was also assessed that 63 sites in the US was not sufficient and that least 75 sites would be needed to meet the enrollment goal. Therefore CO in the US continued to search for additional sites.
In August 2004 CO in EU informed the Study Team that due to the availability of additional resources Germany would be able to conduct this study. It was projected that Germany could contribute 65 patients from 40 sites. The Study Team changed the patient allocation to approximately 40% from the US, 30% from International Countries and 30% from Germany.

Sites in the US were the first one to meet the regulatory requirements to start the study. An investigator meeting was conducted on August 2004. A second Investigator meeting was conducted in October 2004 for the sites which could not attend the meeting in August. On-site training was provided to all sites that could not attend the 2 Investigator Meetings. The first patient was enrolled in October 2004.

During the first quarter of 2005 it was noted that the number of patient enrolled was lower than projected (see graph on page 2). In March 2005, feasibility questionnaires were sent to the GSK CO teams in 2 International countries (i.e., South Korea and South Africa), and 10 EU countries (i.e., Russia, Ukraine, Slovenia, Poland, Latvia, Lithuania, Estonia, Hungary, Czech Republic, Slovakia). Of these 12 countries, 3 countries (i.e., South Korea, Russia and Ukraine) were identified as having the resources to conduct the study and an adequate number of potential patients and were selected. The site contribution from each of these 3 countries was as follows: 4 sites from South Korea, 12 sites from Russia and 3 sites from Ukraine. During this period, the patient allocation was re-assessed and adjusted to become approximately 32% from the US, 36% from International countries and 32% from EU countries.

Sites in International and EU countries were started as soon as they met the requirements of the local regulatory authorities. Investigator meetings were conducted in March 2005 for sites in

India, in April for sites in Argentina, Brazil and Chile, in July 2005 for sites in South Korea, and Sep 2005 for sites in Russia and Ukraine. The CO team in Germany conducted on-site initiation visit between March and July 2005. A "refresher" Investigator Meeting was also conducted in July 2005 for the US sites.

Between October and early December 2005 representatives from the Study Team visited the CO and Clinical teams and investigators in South Korea, India and Russia. The purpose of these visits was to answer questions that they had for LAM100034, discuss the clinical development plan for Lamictal and explore ways to collaborate to conduct future clinical trials."

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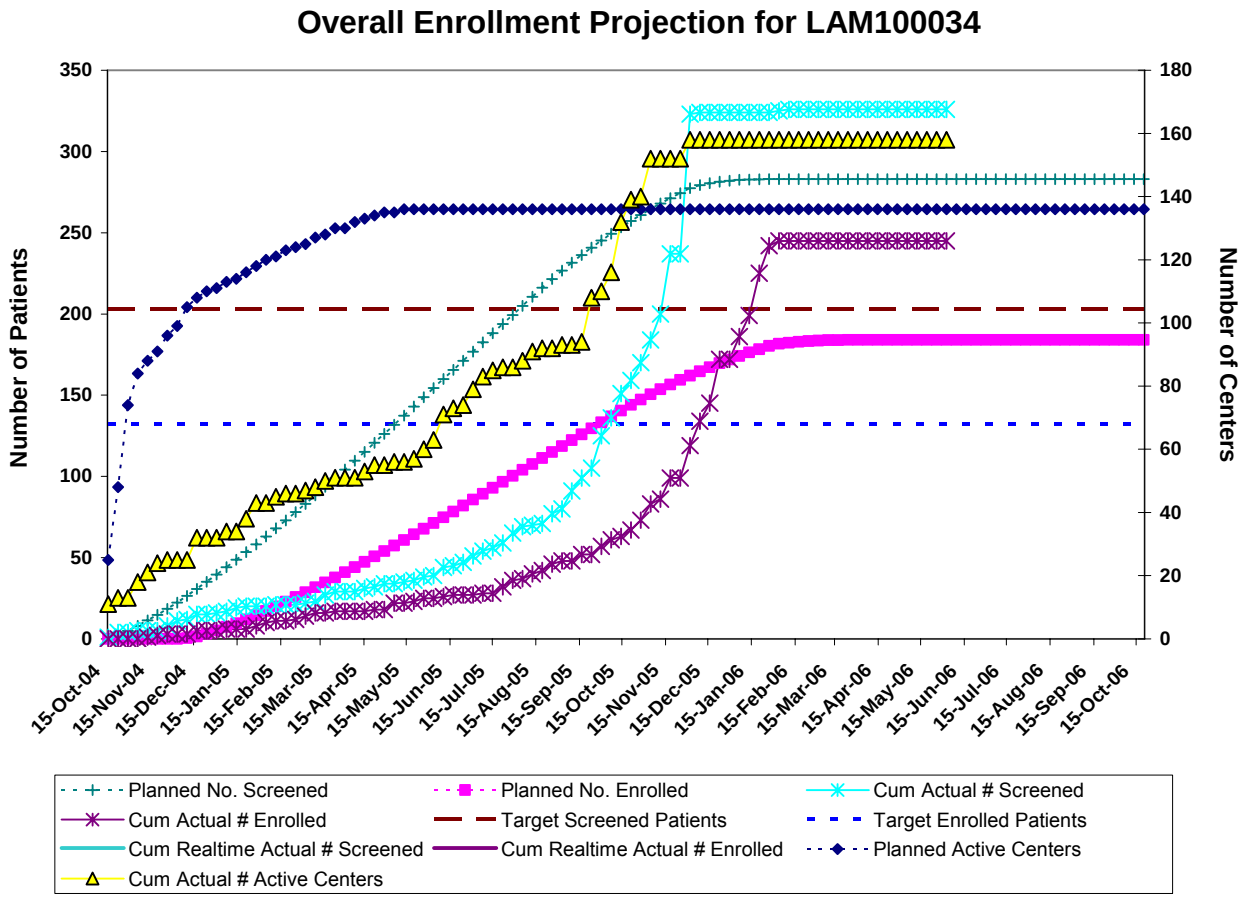
Figure 7 Chronology of Planned and Actual Patient Enrollment in Study LAM100034



- The statistical reviewer conducted an additional analysis of the primary efficacy endpoint for the first 132 patients randomized and found that the overall results (Table 19) for all patients were still statistically significant (p=0.043). However, this level of statistical significance (p=0.043) was at a much lower level than that (p< 0.001) for the primary analysis of all randomized patients included in the modified ITT (MITT) analysis (i.e. had at least one post-treatment efficacy outcome).

Another concern that will be presented and discussed in more depth later in this section relates to the observation (nebulously noted by the sponsor but characterized comprehensively by the statistical reviewer, Dr. Massie) that the treatment effect (lamotrigine XR – placebo) for the primary efficacy endpoint is markedly reduced (i.e. ranging from much smaller to absent, depending on the specific analyses) for patients studied in the U.S sites compared to all non-U.S./foreign sites pooled). Of interest and potential concern, this analysis (Table 19) of the first 132 randomized patients not only showed that the median treatment difference for all non-US sites pooled was approximately 10 fold greater (~ 20 %) vs that of the all U.S. sites (~ 2%), but that the numerical treatment difference for all foreign sites was also much higher, ranging from 12 % to 31 %.

Table 19 Percent Seizure Rate Change from Baseline in First 132 Randomized Patients with Post-Baseline Data

	Randomized treatment group											
	Placebo					Lamotrigine XR						
	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	Median of Differences	Wilcoxon p
Country												
United States	33	3.4	25.6	19.6	54.8	30	3.2	31.7	20.3	54.7	2.27	0.826
All Non-U.S.	36	2.3	29.6	26.6	35.0	33	2.0	54.8	37.6	60.6	20.41	0.015
Brazil	1	3.4	9.8	9.8	.	.	.	.	.	.	.	.
Chile	4	4.6	19.4	17.7	14.3	3	8.6	53.0	31.0	45.9	27.54	0.596
Germany	8	2.3	28.7	19.2	34.9	7	2.0	67.3	40.9	55.7	31.32	0.325
India	6	1.3	39.2	29.4	41.3	8	2.1	63.3	33.4	73.8	15.44	0.478
Korea	15	2.3	23.4	28.4	39.5	10	1.2	50.0	48.8	15.8	16.73	0.157
Russian Federation	2	2.3	60.2	60.2	0.0	5	2.5	72.4	21.4	113.6	12.21	0.845
All	69	2.4	29.3	23.2	45.4	63	2.4	46.8	29.4	58.1	12.07	0.043

- In presenting various subgroup analyses, the sponsor noted that the efficacy response for the primary efficacy endpoint for U.S. patients was lower relative results for patients in the other 8 countries. More specifically the sponsor noted : "The median percent reduction in seizure frequency by country displayed a smaller treatment difference in US subjects as compared to the other 8 countries. In order to assess if US responses were different, the primary endpoint was re-analyzed to include country and a treatment by country interaction." The sponsor then noted that the treatment by country interaction did not show a significant difference (p=0.500, suggesting that there was not an overall difference among amongst **all** countries), and that this analysis indicated that there is a not statistically significant 50% chance that treatments differ between countries. The sponsor further noted that with this model, the overall treatment effect was still significant (p=0.027). Despite this notation, the sponsor did not actually nor directly present the numerically smaller treatment difference observed in the U.S. vs the treatment difference in each country. In contrast, the sponsor presented the results for the primary efficacy endpoint according to 5 change categories (Table 20). This unusual and complex presentation of results for the primary efficacy endpoint presented data

with too many variables (including each treatment in each country) that did not clearly exhibit (but rather obscured/masked) the overall treatment difference of all MITT patients in each country.

Table 20 Summary of Percent Change from Baseline in Weekly Seizure Rate for Entire Study Period According to Country

Type: All Partial Seizures

Country	Treatment Group	n	No.(%) of Subjs Seizure-Free	------Reduction------- >=50%	26-49%	No Change +/- 25%	--------Increase------- 26-49%	>=50%
Argentina	Placebo	3	0	0	1 (33%)	2 (67%)	0	0
	Lamictal XR	1	0	0	1 (100%)	0	0	0
Brazil	Placebo	4	0	0	0	4 (100%)	0	0
	Lamictal XR	1	0	0	0	1 (100%)	0	0
Chile	Placebo	6	0	0	4 (67%)	2 (33%)	0	0
	Lamictal XR	4	0	2 (50%)	0	2 (50%)	0	0
Germany	Placebo	13	0	4 (31%)	3 (23%)	3 (23%)	3 (23%)	0
	Lamictal XR	9	0	5 (56%)	0	2 (22%)	2 (22%)	0
India	Placebo	9	0	2 (22%)	3 (33%)	3 (33%)	1 (11%)	0
	Lamictal XR	16	0	9 (56%)	1 (6%)	4 (25%)	0	2 (13%)
Korea	Placebo	16	0	6 (38%)	2 (13%)	7 (44%)	0	1 (6%)
	Lamictal XR	15	0	6 (40%)	5 (33%)	3 (20%)	0	1 (7%)
Russian Federation	Placebo	23	0	4 (17%)	6 (26%)	11 (48%)	1 (4%)	1 (4%)
	Lamictal XR	23	2 (9%)	11 (48%)	8 (35%)	3 (13%)	0	1 (4%)
Ukraine	Placebo	4	0	1 (25%)	0	2 (50%)	1 (25%)	0
	Lamictal XR	5	0	3 (60%)	0	2 (40%)	0	0
United States	Placebo	42	1 (2%)	12 (29%)	11 (26%)	16 (38%)	1 (2%)	2 (5%)
	Lamictal XR	42	1 (2%)	13 (31%)	14 (33%)	11 (26%)	0	4 (10%)
Total	Placebo	120	1 (<1%)	29 (24%)	30 (25%)	50 (42%)	7 (6%)	4 (3%)
	Lamictal XR	116	3 (3%)	49 (42%)	29 (25%)	28 (24%)	2 (2%)	9 (7%)

In his review, Dr. Massie commented that because many of the foreign countries had only a few/ relatively small number of patients, the analysis/test applied by the sponsor was very likely underpowered. He further thought that it seemed reasonable to conduct a more regional geographic analysis by combining/pooling patients from all South American countries, Brazil (N=5), Chile (N=10), and Argentina (N=4), with small numbers of patients and also from the Ukraine (N=9) with Russian Federation (N=46). This additional, exploratory analysis (in which relatively small numbers of patients enrolled in 5 countries were pooled into 2 regions for comparative analysis amongst all the other relatively larger enrolling countries in different geographic regions) revealed a nominal p-value of 0.21. This p value approached a threshold (p~0.15) generally considered to suggest a notable/"significant" treatment and country interaction in such analyses because significance levels above 0.05 are frequently used for testing interactions considering that tests at the usual level (e.g. p=0.05) may be seriously underpowered. Increasing the significance level generally increases the power (at the expense of type I error).

Dr. Massie further noted that another statistical comparison (via a pooled Rank ANOVA model) exploring an interaction between treatment group and country for all U.S sites vs all non-U.S. sites pooled (an analysis not present by the sponsor) showed that the treatment difference/effect in the U.S. was not only numerically much smaller in the U.S. than that in every other country (Table 21), but also that this treatment and country interaction for U.S. sites vs all pooled foreign sites was statistically significant (p=0.03). Recall, that the results for all randomized patients analyzed by treatment showed that the median % reduction for placebo was 24.2 %, and that for XR was 46.1 %, indicating a median difference of 18.2 % and a clear statistical difference based upon a Wilcoxon p-value of < 0.001.

Table 21 Primary Efficacy Endpoint for ALL Randomized Patients for U.S, Sites vs All Foreign Sites as a Pooled Group and According to Each Foreign County

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

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

- U.S. sites accounted for 87 (36%) of the randomized patients, a number larger than that for any other country (N= 8 foreign countries) in study LAM100034. Although the treatment effect in the subgroup of patients randomized in the U.S. technically favored lamotrigine XR numerically, **this effect did not approach nominal significance (p=0.68) and the median treatment difference was only ~ 3 %. In marked contrast, pooled results of all foreign countries showed that the median treatment effect was much larger (~ 26 %) vs that of the pooled U.S. sites (~ 3 %) and this difference was statistically significant (test for treatment by U.S. vs. non-U.S. interaction: p=0.03) (Table 21).**

- A similar analysis (from Dr.Massie) for U.S. sites vs all pooled foreign sites was conducted for patients who completed the study for ≥ 18.5 weeks (19 weeks ± 0.5 week = planned complete study treatment). This analysis (Table 22) also showed that the median treatment effect/difference was much smaller (~ 10%) for all pooled U.S. sites compared to that (~ 32 %) for all pooled foreign sites.

Table 22 Percent Change of Seizure Rate from Baseline in Completers (≥18.5 weeks of double blind period) For Pooled U.S. Patients vs All Pooled Foreign Patients

{tc "Tabulate " \f C \l 1}{tc "Cross-tabular summary report " \f C \l 2}{tc "Table 1 " \f C \l 3}	Randomized treatment group										Median of Differences	Wilcoxon p
	Placebo					Lamictal XR						
	N	Baseline Median	Median Change	Mean Change	StdDev Change	N	Baseline Median	Median Change	Mean Change	StdDev Change		
Country												
United States	34	2.9	34.1	23.7	55.8	31	2.4	43.9	36.1	39.9	9.69	0.325
All Non-U.S.	66	2.0	15.8	16.7	46.1	59	2.3	51.4	48.1	39.3	32.10	<0.001
All	100	2.0	23.8	19.1	49.5	90	2.3	49.0	43.9	39.7	24.04	<0.001

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

- The statistical review also described another interesting finding. The post-hoc, unblinded analysis of efficacy results of the first 37 patients who patients were randomized in the U.S (N=84 total) did not suggest efficacy of the treatment. No other countries enrolled patients during the approximately 9 months that it took to enroll these 37 U.S. patients. The estimated treatment difference for the median result for approximately the first half (N=41) of the patients randomized in the U.S. is ~ 4 % (Table 23). The estimated treatment difference in the second half of the U.S. patients is identical (~ 4 %). The numerical treatment difference for a similar number of patients from foreign sites in respective analyses was numerically much higher than that for patients from U.S. sites (Table 23). The statistical reviewer speculates that if one had access to the unblinded data from the first 37 patients, such results could potentially have suggested that increasing the sample size and possibly enrolling patients from non-U.S./foreign countries, and if such sample size re-estimation was done, it would require a p-value adjustment to protect the type I error. However, the sponsor had responded that it did not unblind the results nor conduct an unplanned interim analysis and re-estimate the sample size.

Table 23 Comparison of Treatment Effect on Percent Change in First 40 Randomized Patients versus Next 40 Patients for U.S. and non-U.S Sites

Country	Randomized treatment group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	Median of Differences	Wilcoxon p
First 40 Non-U.S.	22	1.5	29.9	27.1	36.3	18	2.1	62.7	42.4	57.6	25.60	0.0388
Last 42 Non-U.S.	21	2.4	38.2	31.4	37.4	21	2.1	49.5	38.6	58.6	14.51	0.2370
First 41U.S.	22	3.4	35.5	20.6	64.0	19	2.4	34.9	27.1	48.6	3.74	0.7640
Last 43 U. S.	20	1.9	25.2	28.3	32.7	23	2.6	42.1	26.9	51.8	4.13	0.6436

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

Nevertheless, it is conceivable that a blinded review of the primary efficacy results (and comparison to analyses derived from previous results with immediate-release lamotrigine) could have shown the distribution of efficacy results and potentially have suggested whether there is little or not much of a treatment effect for XR lamotrigine based upon this preliminary "blinded" assessment. This seems true particularly if the blinded, pooled results showed that the distribution of results was relatively limited/narrow and not trending toward a separation as would be expected for treatment groups with different effects. Considering that the sponsor has extensive experience with controlled trial results, especially with epilepsy treatment, it would not be surprising if the sponsor could look at "blinded" preliminary seizure results and have insight into whether the treatment might be effective. Based upon conversations with the Statistical Team Leader, Dr. Kun Jin, he is concerned that a careful review and analysis of '"blinded" efficacy results can give insight into whether a study treatment is exerting a substantial effect on the outcome measure. Thus, it is possible that the sponsor conducted such an analysis and did not admit to doing so.

- **Of greater importance, these results from all pooled U.S. patient sites raise the most serious question of whether this new, extended-release formulation of lamotrigine is effective as adjunctive treatment of partial epilepsy in adults in the U.S.** There is no clear explanation for this observation that raises a serious concern about approval of XR lamotrigine at this time. One potential explanation might be related to a pharmacokinetic (PK) differences between the IR and XR formulations and also possible pharmacodynamic (PD) effects as a result of some PK differences. The PK "shape of the curve" is quite different and XR lamotrigine could theoretically produce different PD effects than that of IR lamotrigine. Whereas the time to Tmax ranges between 1-5 hours with IR lamotrigine, the time to Tmax with XR is much longer/delayed and also varies somewhat with the type of concomitant AED, EIAEDs (4-6 hrs), VPA (9-11 hrs), and "neutral" AEDs (6-10 hrs) that do not alter plasma lamotrigine levels. Table 24 shows data comparing Cmax, AUC, and Cmin for the IR vs XR formulations, specifically the ratio of XR/IR and the 90 % confidence interval of these ratios. Whereas the XR/IR ratio for AUC is similar (~ 1) for VPA and "neutral" concomitant AEDs, this ratio for EIAEDs is ~ 0.8 (e.g. ~ 20 % reduced vs IR). Of

perhaps greater import, there is a mean reduction in Cmax (11-29 %) for XR for all concomitant AEDs , with the most marked reduction associated with the use of EIAEDs. Related to this observation, the Clinical Pharmacology Reviewer (Dr. Veneeta Tandon) noted in the label (based upon data from the converting identical doses of IR to XR) : "However, in some subjects receiving enzyme-inducing AEDs, a reduction in Cmax of 45-77% was also observed."

Considering that it is not clear if the anti-epileptic efficacy of lamotrigine is related to Cmax and/or AUC, (and/or perhaps PK "shape of the curve"), it is possible that these PK differences related to lower Cmax and "PK shape" of the curve could contribute to lower efficacy of XR vs IR and perhaps explain at least in part the poor efficacy of XR in U.S. (vs non-U.S.) patients. Although the Clinical Pharmacology review did not analyze and present any PK parameter analyses of U.S. vs non-U.S., this review did indicate that the distribution of plasma lamotrigine concentrations appeared to be overlapping (Figure 2 shown in section 5.3 Exposure-Response Relationships).

Table 24 Steady-State Bioavailability of Lamotrigine XR Relative to Immediate-Release Lamotrigine at Equivalent Daily Doses (Ratio of XR to IR 90% CI

Concomitant AED	$AUC_{(0\text{-}24ss)}$	C_{max}	C_{min}
EIAEDs*	0.79 (0.69,0.90)	0.71 (0.61,0.82)	0.99 (0.89,1.09)
VPA	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
AEDs other than EIAEDs* or VPA	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

* EIAEDs include carbamazepine, phenytoin, phenobarbital, and primidone.

There were also some noteworthy differences in the % of the various concomitant AED groupings for XR lamotrigine-treated patients in the U.S. group vs the non-U.S. group. Table 25shows that the U.S. patients had a lower % with VPA alone or with "neutral" AEDs (7 % vs 27 %), a lower % with VPA with EIAEDs (2 % vs 8 %), a higher % with EIAED alone or with "neutral" AEDs (57 % vs 47 %) and a higher % with "neutral" AEDs (33 % vs 18 %). Overall, this imbalance may have biased U.S. patients toward experiencing lower plasma lamotrigine levels.

Table 25 Summary of Number of AED Concomitant AED Medication Groups According to U.S. Sites vs Non-U.S. Sites

		Placebo (N=120)		Lamictal (N=116)	
	Number of AEDs	US Sites (N=42)	Non-US Sites (N=78)	US Sites (N=42)	Non-US Sites (N=74)
Number of AEDs	n	42	78	42	74
	1 AED	18 (43%)	31 (40%)	21 (50%)	38 (51%)
	2 AEDs	23 (55%)	47 (60%)	21 (50%)	36 (49%)
	3 AEDs	1 (2%)	0	0	0
AED Group	VPA/DVS with EIAEDs	5 (12%)	19 (24%)	1 (2%)	6 (8%)
	VPA/DVS alone or with non-EIAEDs	5 (12%)	14 (18%)	3 (7%)	20 (27%)
	EIAEDs alone or with non-inducing/inhibiting AEDs	16 (38%)	27 (35%)	24 (57%)	35 (47%)
	All other regimens	16 (38%)	18 (23%)	14 (33%)	13 (18%)

- Another potential possibility for the explanation of this different effect (U.S. vs foreign sites/patients) could be related to using a less reliable baseline period for characterizing baseline seizure rate if foreign sites were associated with a higher % of patients who used the abbreviated prospectively collected baseline period (i.e. 4 weeks historical seizure rate plus a 4 week prospective baseline) than the % who used the theoretically more reliable, prospectively collected 8 week baseline period for comparison with post-treatment seizure reduction rates (relative to "baseline"). Despite the fact that all patients who were allowed to use a historical baseline were supposed to have provided an adequate diary of seizure results for 4 weeks, it is possible that this issue may have contributed to the different effect in U.S. vs foreign sites.

  In non-U.S. sites approximately one third of randomized patients also used a historical baseline seizure rate and proportion was similar in each treatment group (Table 26). Approximately a quarter of U.S. patients used a historical baseline and there was a slightly higher percentage of these patients who were treated with XR lamotrigine (vs placebo).

  Dr. Massie investigated the effect of using the historical baseline in conjunction with the last 4 weeks prospective baseline vs the baseline seizure rate based only on the last 4 prospectively collected data (Table 27). The proportion of patients that used the historical data option was 34% (31% for Lamotrigine XR and 37% for Placebo) outside the U.S. and 24% (19% for Lamotrigine XR and 29% for Placebo) in the U.S. sites. Outside the U.S., the median baseline seizure rate was 2.0 for patients that had 8 weeks of prospective baseline and 2.2 for patients that had 4 weeks prospective and 4 historical seizure rate data. Thus, the historical data did not seem to alter seizure rates vs rates. In the U.S., the median baseline seizure rate was 2.3 for patients that had 8 weeks of prospective baseline and 3.3 for patients that had 4 weeks prospective and 4 historical data. Thus, historical data appeared to increase the rate substantially compared to the rate determined solely from the last 4 weeks of prospectively collected data.

  To investigate if the primary analysis result is dependent on the use of historical baseline data, Dr. Massie analyzed the on treatment data relative to a baseline seizure rate determined

from the last 4 weeks prospectively collected baseline period that was collected for all patients. The results for the percent change from baseline using only the last 4 weeks of the baseline period for the baseline seizure rate are shown in Table 28 for each country and for U.S. vs non-U.S. sites, and also for all randomized patients. The results are reasonably similar to the results for the primary analysis (for all randomized patients, as well as for the first 132 randomized patients) that permitted the use of 4 weeks of historical baseline seizure data for some patients. Therefore, allowing the use of historical data for calculating baseline seizure rates for half of the baseline period does not seem to have had any noteworthy effect on the primary analysis of the primary efficacy endpoint and certainly does not explain the lack of efficacy in U.S. patients.

Table 26 Use of 4 Week Historical Baseline Along with 4 Week Prospective Baseline for Baseline Seizure Rate According to Treatment and U.S. vs Non-U.S. Grouping

			Randomized Treatment Group	
			Lamotri-gine XR	Placebo
Country	**Historical Baseline Used**			
Non-US	**No**	**N**	52	50
		Percent	67.53	63.29
	Yes	**N**	25	29
		Percent	32.47	36.71
US	**No**	**N**	36	31
		Percent	81.82	72.09
	Yes	**N**	8	12
		Percent	18.18	27.91

Table 27 Baseline Seizure Rate Based Upon Last 4 Weeks Prospectively Collected Data Versus 4 Week Prospectively Collected Baseline AND 4 Week Historical Baseline Seizure For U.S. and Non-U.S. Patients

		Baseline Seizure Rate Including Historical				Baseline Seizure Rate in Last 4 weeks (Excluding Historical)			
		N	Mean	Median	StdDev	N	Mean	Median	StdDev
Country	**Historical Baseline Used?**								
Non-US	**No**	101	4.1	2.0	6.8	101	4.3	1.9	7.3
	Yes	53	3.4	2.0	3.7	53	3.4	1.9	3.6
US	**No**	65	6.1	2.4	11.3	65	5.7	2.2	10.1
	Yes	20	5.3	3.4	7.1	20	6.7	3.5	12.2

Table 28 Percent Change from Baseline in All Randomized Patients Using Only Last 4 Prospective Weeks of Baseline Period According to U.S. or Non-U.S. Patients and Each Country

	Randomized Treatment Group											
	Placebo					Lamotrigine XR						
	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	Median of Differences	Wilcoxon p
Country												
United States	42	2.4	29.9	21.3	47.3	42	3.0	37.2	21.1	59.5	4.91	0.601
All Non-U.S.	78	1.7	18.2	9.2	56.8	74	2.4	44.1	36.6	52.0	26.86	<0.001
Argentina	3	1.4	-39.1	-27.7	41.3	1	2.4	23.7	23.7	.	62.83	0.371
Brazil	4	2.2	16.5	15.1	23.1	1	2.4	7.7	7.7	.	-8.78	0.724
Chile	6	4.1	10.4	-23.1	101.6	4	7.1	34.5	33.0	25.5	18.02	0.241
Germany	13	2.4	43.9	22.7	51.7	9	2.2	74.6	46.3	54.6	31.93	0.317
India	9	1.2	22.1	14.6	49.6	16	2.4	44.0	23.1	66.7	12.85	0.412
Korea	16	1.9	25.8	22.7	49.3	15	1.4	42.6	34.2	37.6	9.07	0.363
Russian Federation	23	1.9	12.8	2.4	61.4	23	2.2	45.5	45.2	57.8	42.06	0.010
Ukraine	4	1.6	2.5	7.7	34.0	5	2.9	50.9	41.2	35.5	36.71	0.270
All	120	2.2	21.8	13.4	53.8	116	2.4	40.0	31.0	55.1	18.28	0.002

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

- Dr. Massie also analyzed the data to assess the effect of treatment on the absolute change in seizure rate from baseline. Table 29 shows these results for all randomized patients with post-baseline data for U.S. vs non-U.S. sites, for each country, and for all sites combined.

Overall (with the exception of Brazil that had 5 total patients (1 XR, 4 placebo), the magnitude of the median treatment difference and generally the p value were similar in this analysis vs the primary analysis shown in Table 21.

- In response to an inquiry, the sponsor informed me that noted approximately 75 % of the patients in the clinical development program for randomized, double-blind, placebo-controlled studies (711 patients treated with lamotrigine and 419 with placebo) supporting the initial approval or IR lamotrigine were patients studied in the U.S. This contrasts with the vast majority of patients in this study (LAM`00034) being from foreign sites.

- The U.S. data "lack" of efficacy cannot simply be explained by the placebo response in U.S. sites. Although the median % reduction of seizure rate from baseline for placebo patients in the U.S. sites is relatively high (~ 33 %) compared to non-U.S. sites (~ 23 %), other countries (India – 30 %, Germany – 28 %, Korea – 32 %, Chile – 28 %) that showed much greater treatment differences/effects also showed relatively high placebo response. Altogether, these 4 other foreign countries (N=88) accounted for a similar number of randomized patients in the MITT analysis as the U.S. sites (N= 84).

- It is interesting to compare the response described in label for IR lamotrigine with that for XR lamotrigine. The label for IR lamotrigine describes the approval (for adjunctive treatment of partial epilepsy in adults) based upon 3 studies all of which used the median % reduction from baseline seizure rate as the primary efficacy endpoint. The largest pivotal study (N=216, treated for 24 weeks) supporting approval was a parallel group study consisting of patients randomized to one of three treatments (~ 1/3 to each group) including placebo or a fixed daily dose of 300 or 500 mg lamotrigine. In this study, the % was 8 for placebo, 20 % for 300 mg/d, and 36 % for 500 mg/day. Efficacy (28 % = arithmetic median difference = IR lamotrigine % - Placebo %), based upon statistical significance, was shown only in the 500 mg group. Another pivotal study (cross-over, involving 14 weeks separate treatment for placebo and lamotrigine, with 4 week washout between treatments), conducted in the U.S., showed a statistically significant difference with a 25 % reduction for lamotrigine (400 mg/d = target dose) vs placebo (however, the label does not clarify what is the treatment response for each treatment or if this is the treatment difference). The smallest study (N=41), supporting approval in the label, was a 12 week cross-over design (with 4 week washout) for each treatment (N=28 on a concomitant AED other than VPA and receiving 300 mg/d lamotrigine; N=13 on VPA and receiving 150 mg/d lamotrigine) conducted in the U.S.. This study also showed a statistically significant difference with a 26 % reduction for lamotrigine vs placebo (however, the label does not clarify what is the treatment response for each treatment or if this is the treatment difference). Of note, all these studies were based upon results collected in the U.S. (that contributed the vast majority of positive efficacy data) or in the U.K. a location for which there is typically no serious question about the quality of clinical data.

  It is also difficult also to know whether the explanation for the lack of efficacy in U.S. sites may be related to daily lamotrigine dose and concomitant AED class/group to any extent rather than mainly to differences in the amount of data collected in the U.S. The label did not

note that vast majority of patients (derived from the first 2 pivotal studies described that were conducted in the U.S) who supported the approval of IR lamotrigine and who exhibited statistically significant therapeutic differences (when randomized to 500 or 400 mg daily . I believe that these patients were not using VPA but were predominantly using an EIAED because at the time that these studies were conducted, an EIAED was the typical AED used as adjunctive treatment.

- I have also noted in section 5.3 (Exposure-Response Relationship) my concern that no appropriate exposure-response relationships have been conducted and presented.

- Dr. Massie conducted an analysis also assessing the pre-and post-randomization seizure rate data to show the absolute change (Δ) from baseline for weekly seizure rate in all randomized patients, according to U.S. vs non-U.S. sites, and according to each country. These results are shown in Table 29. Of interest, despite the fact that the median change seizure rate (0.8 decrease) for XR was similar for patients from U.S. vs non-U.S. sites, the median change for placebo is much higher for U.S. patients is identical to that for XR treatment and is much greater than that for placebo (0.4 decrease) for non-U.S. sites. Although the mean change is quite different for XR and much greater (2.7 decrease) for U.S. sites than that (1.4 decrease) for non-U.S. sites, the p values for these data were strikingly different, indicating a highly statistically significant difference for non-U.S. sites and a p-value suggesting no difference at all for U.S. sites. This analysis also suggested "numerical efficacy" based upon a substantial numerical treatment difference for median absolute change (Δ) from baseline for seizure rate all foreign countries except Chile and Korea.

Table 29 Absolute Change (Δ) from Baseline for Weekly Seizure Rate in All Randomized Patients (MITT, Study LAM10034)

	Placebo					LAMOTRIGINE XR						
Country	**N**	**BaseMedian**	**Median Δ**	**Mean Δ**	**StdDev**	**N**	**BaseMedian**	**Median Δ**	**Mean**	**StdDev**	**Median Difference**	**Wilcox p**
United States	42	2.4	0.8	0.8	3.7	42	2.6	0.8	2.7	7.8	0.05	0.9039
All Non-U.S.	78	2.0	0.4	0.2	2.7	74	2.2	0.8	1.4	2.7	0.53	0.0012
Russian Federation	23	2.0	0.2	0.3	1.6	23	2.1	1.0	2.3	3.5	0.93	0.0069
India	9	1.1	0.4	-2.1	7.2	16	2.1	0.9	0.7	1.3	0.81	0.0253
Brazil	4	2.3	0.2	0.3	0.1	1	2.9	0.6	0.6	.	0.40	0.2888
Germany	13	2.3	0.5	0.8	1.6	9	2.0	1.1	1.1	1.6	0.45	0.5932
Ukraine	4	1.5	0.0	0.1	0.5	5	3.1	1.1	0.6	1.4	0.99	0.7133
Korea	16	2.3	0.6	0.6	0.9	15	1.6	0.6	1.2	3.2	0.08	0.7369
Chile	6	4.4	0.9	1.0	0.8	4	5.8	0.5	1.3	3.3	-0.33	0.7491
Argentina	3	2.0	0.0	0.2	0.6	1	2.5	0.7	0.7	.	0.67	1.0000
All	120	2.1	0.5	0.4	3.1	116	2.3	0.8	1.9	5.2	0.36	0.0094

Generated by Dr. Tristan Massie, Primary Statistical Reviewer

- In an additional analysis, Dr. Massie presented data (for all randomized patients from **all** countries/sites) suggesting that efficacy is not maximally achieved soon after achieving PK steady state (i.e. at the end of 7 weeks after initiating XR lamotrigine treatment in this study or ~ 1 week after starting the maximal dose at the beginning of week 7). PK steady state with multidosing is expected within approximately 1 week considering that the elimination half-life for lamotrigine is ~ 24 hours. In contrast, these results shown in Table 30 seem to suggest that efficacy may progressively increase throughout the treatment period (especially up to week 15, ~ 7 weeks after theoretically achieving PK steady state). These interesting results suggest the possibility that pharmacodynamic anti-seizure effects are not immediately achieved soon after achieving PK steady state.

Table 30 Percent Change from Baseline by Visit in Study for all Randomized Patients

Visit number(Week)*	Randomized Treatment group											
	Placebo						Lamictal XR					
	Percent Change						Percent Change					
	N	Median	StdDev	Mean	Min	Max	N	Median	StdDev	Mean	Min	Max
4 (Week 3)	120	6.4	64.1	-4.8	-278	100.0	112	16.6	71.9	6.6	-311	100.0
5 (Week 7)	117	15.6	48.6	10.4	-228	100.0	106	32.4	57.3	22.4	-253	100.0
6 (Week 11)	112	16.1	44.4	15.6	-185	100.0	99	40.0	45.2	34.2	-166	100.0
7 (Week 15)	108	17.0	45.9	18.5	-206	100.0	98	43.0	42.5	38.5	-134	100.0
8 (Week 19)*	108	21.3	47.0	19.5	-231	100.0	97	48.9	41.9	42.0	-110	100.0

*Actual visit time may be slightly different. For this analysis observed visit times were allocated to the closest protocol planned visit.

- Dr. Massie also conducted an analysis exploring efficacy for the primary efficacy endpoint based upon concomitant AED grouping for all randomized patients. The median treatment difference was 12 % for EIAEDs alone or with "neutral" AEDs (N=59), 15 % for "neutral" AEDs, 28 % for VPA alone or with "neutral" AEDs (N=23), and 37 % for VPA with EIAEDs (N=7) (Table 31). Wilcoxon p-value for each concomitant AED grouping ranging from 0.005 to 0.260. Dr. Massie further noted that, overall, there is limited power to test for differences in efficacy between the concomitant AED type groups because some of the group sizes are quite small. Nevertheless, he suggested that it is not possible to conclude that there are significant differences (nominal p=0.28) in efficacy depending on the AED type grouping.

  Dr, Massie also explored the effect of this variable (i.e. concomitant AED type/class grouping) on the primary efficacy endpoint for U.S. vs non-U.S. sites. The median % seizure rate reduction (from baseline) ranged from ~ 19 to 41 % for all concomitant AED groupings for non-U.S. sites. Respective p-values for these analyses suggested or approached nominal statistical significance ranging from 0.002 to 0.207 (VPA with EIAEDs = 0.002; VPA alone or with "neutral" AEDs = 0.023; EIAEDs alone or with "neutral" AEDs = 0.053; "neutral" AEDs = 0.207) . In contrast, analogous analyses for U.S sites did not suggest much, if any, numerical efficacy. The median % seizure rate reduction (from baseline) ranged from ~ 3 to 9 % for all concomitant AED groups for U.S. sites. These respective p-values ranged from 0.751 to 1.00 (EIAEDs alone or with "neutral" AEDs = 0.751; VPA alone or with "neutral" AEDs = 0.766; "neutral" AEDs = 0.983; VPA with EIAEDs = 1.00).

Table 31 Effect on Percent Change in Seizure Rate by Concomitant AED Type/Grouping in All Randomized Patients

	Randomized Treatment Group										Median of Differences	Wilcoxon p
	Placebo					Lamictal XR						
	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change	N	Baseline Median	Median %Change	Mean %Change	StdDev %Change		
AED TYPE												
EIAEDs alone or with non-inducing/inhibiting AEDs	43	2.0	25.6	23.6	34.6	59	2.5	42.1	33.4	43.5	11.70	0.081
VPA/DVS with EIAEDs	24	2.1	21.3	19.1	30.4	7	1.8	65.9	57.2	24.2	36.84	0.005
VPA/DVS alone or with non-EIAEDs	19	2.3	29.3	27.5	27.3	23	2.6	54.8	40.8	67.9	27.67	0.035
All other regimens	34	3.1	17.8	10.9	70.6	27	1.9	36.8	27.1	53.0	14.68	0.260

- I also questioned whether there was any difference in the frequency of partial seizure types during treatment. The sponsor had presented the frequency of the various seizure types at baseline but had not presented any the frequency of partial seizure types during treatment. In response to my inquiry, the sponsor provided information on the frequency of various partial seizure types occurring during treatment and also new partial seizure types (not present at baseline) occurring during treatment. There did not appear to any noteworthy change in the type of partial seizures occurring during treatment (vs at baseline) nor in the frequency of new partial seizure types developing during treatment.

Subgroup Analyses

The sponsor did not present analyses according to % change for primary efficacy endpoints for standard subgroup analyses (e.g. gender, race, age) but instead presented treatment group analyses according to categorical efficacy responses (i.e. $\geq$ 50 % decrease, 26-49 % decrease, no change such as $\pm$ % 25 increase or decrease, $\geq$ 50 % increase, 26-49 % increase). Consequently, the following subgroup analyses (e.g. gender, race, age) for the primary efficacy endpoint were performed by the primary statistical reviewer, Dr. Massie. These analyses essentially agreed with the analyses and conclusions of the sponsor for these subgroups.

Gender

Approximately 50% of patients were male and female. There was a suggestion of efficacy in both genders (nominal significance level was reached) and there was no compelling evidence that the treatment effect was larger in one gender subgroup than the other (Table 32).

Table 32 % Change in Baseline Seizure Rate at End of DB Phase by Gender

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

Interaction test p= 0.9104

Race

The proportions of patients of each race were as follows: 68% were recorded as White, 12% were recorded as East Asian, 11% were recorded as South or Central Asian, and 9% were others (including African Americans, Alaskan or Native Americans, South East Asians, and Mixed). The non-White subgroups were too small to permit reliable estimates of treatment differences between races. There were no clear race differences (Table 33).

Table 33 % Change in Baseline Seizure Rate at End of DB Phase by Race

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

Interaction test p= 0.9471

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

Age

Ages ranged from 13 to 73 and the mean and median ages were about 36. Less than 5% of patients were 65 or older. Approximately 10% of patients were ≤ 18 years old and approximately

4 % of patients were < 16 years old. Treatment group differences were nominally significant in both subgroups in favor of lamotrigine XR and there was no compelling evidence that the treatment difference was larger in one age group than the other (Table 34).

Table 34 % Change in Baseline Seizure Rate at End of DB Phase by Age Group

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

Interaction test p=0.2197

6.1.5 Clinical Microbiology

- Not applicable.

6.1.6 Efficacy Conclusions

Sponsor Efficacy Conclusions

• The median percent reduction from Baseline in all partial seizure frequency during ,the entire Treatment Phase was greater in the LTG XR group (46.1%) than in the placebo group (24.2%) (p=0.0004) for the ITT Population.

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

• The percentage of subjects who showed a ≥50% reduction in all partial seizure frequency over the entire Treatment Phase was greater in LTG XR group (42.2%) compared with the placebo group (24.2%, p=0.0037) for the ITT Population.

• Time (in weeks) to ≥50% reduction in seizure frequency for the entire Treatment Phase was shorter for the LTG XR group compared with the placebo group (p=0.0007) for the ITT Population. Statistical significance was seen as early as Day 18 (p=0.0448).

• There were differences in the ITT Population between the two treatment groups in the frequency distribution of the investigator's global assessment of subjects' overall clinical status in favor of LTG XR (p=0.0012).

• No effect of race, age, country, AED group, gender or historical baseline use on percent change from Baseline in any seizure type during the entire Treatment Phase was observed.

Statistical Reviewer (Dr. Tristan Massie) Conclusions

The following summary (bolded type added by me for emphasis) in italics was abstracted from the Executive Summary of the statistical reviewer, Dr. Massie.

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

Reviewer Conclusions :

- XR lamotrigine was statistically superior to placebo based upon all randomized data from patients at all sites (N=236) for the MITT primary analysis of the primary efficacy endpoint.

- **A major concern identified during this review is the apparent lack of efficacy for XR lamotrigine for the primary efficacy endpoint in patients treated in U.S. sites.** I view this concern, for which there is no readily apparent explanation, as an extremely serious problem making it difficult to consider XR lamotrigine as effective for an approval action. My concern is particularly heightened considering that a substantial portion (N=84; 36 %) of efficacy data for all randomized patients with post-randomization efficacy data was derived from patients treated in U.S. sites.

  This apparent lack of substantive numerical efficacy in patients in U.S. sites is extremely unusual based upon the experience of Dr. Kun Jin, (Statistical Team Leader) and that of the primary statistical reviewer, Dr. Tristan Massie, who played an instrumental role in providing various analyses that did not show much, if any efficacy for U.S. sites. Although the sponsor had noted that there was reduced efficacy in the U.S. data, the sponsor did not clearly present nor describe results of these data. In contrast, Dr. Massie conducted numerous various analyses of efficacy (especially for the primary efficacy endpoint) that indicated markedly reduced efficacy in the U.S. vs data from all foreign sites combined and also each other foreign country (including country data derived from a relative small number of patients). Dr. Massie's various efficacy analyses were based upon his own exploratory initiatives as discussions I had with him about this issue.

  I am not aware of any Agency approvals for an NME or for new indication for a previously approved drug that occurred in the face of no substantive numerical efficacy in patients from U.S. sites (vs other foreign data) when these primary efficacy data

contributed to a substantial proportion of primary efficacy data for all randomized patients. In fact, the DNP issued an approval letter to the sponsor (GSK) for ropinirole for the new indication of treatment of restless leg syndrome (RLS) because the U.S. study did not demonstrate efficacy of ropinirole that was shown only with foreign data.

I recently became aware that the DPP approved (5/07) an extended release formulation of quetiapine (NDA 22047, Seroquel XR) for treatment of schizophrenia in the face of one positive foreign study that demonstrated efficacy despite the fact that 2 other, randomized, double-blind, placebo-controlled U.S. studies were negative and did not adequately demonstrate efficacy for the new formulation of Seroquel XR. Immediate release Seroquel had been approved previously for treatment of schizophrenia. However, the situation with the approval of this extended release formulation is quite different than that for our situation. In NDA 22047, each study also included one or more treatment arms for immediate release Seroquel (U.S. approved product) as a comparator. It is important to note that immediate release Seroquel clearly showed statistically efficacy (vs placebo) in the foreign study but did not show efficacy in either of the U.S. studies. Thus, the absence of statistical superiority of the approved comparator product in the U.S. studies showed that these studies did not have assay sensitivity whereas, the foreign study did have assay sensitivity. Unfortunately, there was no inclusion of immediate release lamotrigine in study 34 to be able to indicate if there was no assay sensitivity with the U.S. data but assay sensitivity (statistically superiority of immediate release lamotrigine vs placebo) with the foreign data.

Generally, data derived from patients treated in U.S. sites are considered to be the most reliable or desirable data, compared to foreign data, especially data obtained outside of Canada and western Europe as a whole. In this situation, the majority of foreign data (N=130 patients; 55 % of all data) was derived from foreign countries (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina) for which we have relatively little or limited experience for trusting the quality and reliability of these data.

- I consider the pending results of DSI inspections of 2 Korean sites (not received as of 9/14/07) as potentially capable of being a surrogate concern signal for all foreign data and potentially capable of providing a reason questioning the validity of the foreign data as a whole (pending other potential DSI inspections of other foreign sites). However, I would not necessarily consider that DSI inspection reports that do not indicate or suggest a concern about the quality of reliability of the efficacy data in these Korean sites as evidence supporting the reliability and quality of efficacy data in the other foreign sites.

  These 2 Korean sites were selected for DSI inspection for several reasons including the facts that : 1) these sites were the highest enrolling sites (N=26) accounting for 11 % of all randomized patient data; 2) data from these sites suggested efficacy of XR lamotrigine; and 3) there were no relatively large enrolling U.S. sites (none enrolled > 6 patients and most U.S. sites enrolled a few patients, generally < 4 patients/site) for DSI inspection.

Of significant concern,, shortly prior to the PDUFA action date, on 9/14/0 I received a sponsor communication (9/10/07 cover letter) noting that its internal, quality control inspection of the 2 Korean sites scheduled for DSI inspection had identified several, various errors (including errors related to seizure rate efficacy data) in transcribing information from source documents to CRFs at both Korean sites. This letter is presented in section 4.4 (Data Quality and Integrity).

It does not seem possible to assess yet (at least for me) how important **these problems/errors/deficiencies detected BY THE SPONSOR** at both of these Korean sites are. However, these discrepancies/errors related to seizure data collection certainly seem to raise a potential red flag not only about data (especially efficacy data) collected at these Korean sites, but also potentially at many other foreign sites not yet inspected (nor planned at this time for inspection) by anyone.

From my perspective. this summary report by the sponsor does not seem to help the sponsor in any way but instead seems to raise more questions about the quality of the foreign data collected (especially in the foreign sites collected outside of Germany). One wonders if errors discovered at this site are the "tip of the iceberg" relative to numerous other potential errors at other foreign sites not inspected. Furthermore, if the sponsor sends a submission including these reanalyses immediately prior to the PDUFA date next week, we will not be able to review these reanalyses adequately prior to the PDUFA date.

- Numerous, sensitivity analyses of efficacy were robust in clearly supporting the observation that XR lamotrigine is highly effective in foreign sites/patients but not in U.S. sites/patients, who contributed nearly 40 % of the efficacy data. The absence of data suggesting at the least, reasonable, numerical efficacy in U.S patients is a serious concern precluding the overall conclusion that XR lamotrigine is effective as adjunctive treatment of partial seizures in adults. The concern about the demonstration of efficacy (based upon the lack of efficacy in U.S. patients) was not allayed by the efficacy demonstrated in foreign sites/patients because the vast majority of foreign patients were treated in locations (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina) for which we do not have adequate/sufficient experience to be confident in the quality of clinical data collected.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Overview of Safety Data Obtained from Clinical Trials of Immediate-Release Lamotrigine in Subjects with Epilepsy

The following overview of all lamotrigine safety experience is taken from a sponsor summary.

Over 13,000 adult and pediatric subjects have been exposed to lamotrigine IR in clinical trials evaluating the safety and efficacy of lamotrigine IR in the treatment of epilepsy. From these trials, a consistent safety profile has been developed for lamotrigine IR therapy in subjects with epilepsy.

Epilepsy Clinical Trials in Adults. Over 10,000 adult subjects have received lamotrigine IR in adjunctive Phase II-IV clinical trials. The most frequently reported AEs were dizziness, headache, diplopia, ataxia, and nausea. Analyses of vital signs and clinical laboratory data have revealed no undesirable effect of lamotrigine.

Epilepsy Clinical Trials in Pediatric Subjects. Over 2000 pediatric subjects (≤12 years of age) have received lamotrigine IR in Phase II and III adjunctive studies. Overall, the sponsor noted that types of AEs were similar to those reported in adults. The five most frequently reported AEs were infection, rash, somnolence, vomiting, and reaction aggravated (seizure exacerbation). There were no clinically significant changes in any measured clinical laboratory value, nor were there any untoward effects on vital signs or weight.

Rash in Epilepsy Clinical Trials. The most concerning AE associated with the use of lamotrigine has been rash. Although most of these are simple morbilliform rashes without evidence of systemic involvement, serious cutaneous reactions, including Stevens-Johnson Syndrome, have also been reported. The sponsor noted that there is evidence suggesting that exceeding currently recommended dosage and escalation guidelines and coadministration of VPA are risk factors for the development of non-serious and serious rash with lamotrigine.

Analysis of Adverse Events
Adverse events were coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for all studies.

The incidence of treatment-emergent AEs (TEAEs) and drug-related TEAEs were summarized by preferred term within system organ class for each treatment group. A TEAE was defined as any event that had increased in intensity from the baseline phase or had an initial onset during the treatment period. All events for subjects in the LAM100034 Continuation Phase who were randomized to lamotrigine XR in the blinded phase were to be considered treatment-emergent unless they occurred with the same intensity during the baseline phase of the study. For those randomized to placebo, events that emerged in the blinded phase and carried over into the Continuation Phase were not considered treatment-emergent unless they increased in intensity from the baseline or placebo blinded phase. Considering that LAM100036 subjects were not unblinded, all events for subjects in the LAM100036 Continuation Phase were considered treatment-emergent unless they occurred with the same intensity during the baseline phase.

A composite TEAE term of "All Rash" was constructed. In the clinical pharmacology studies in healthy volunteers, terms comprising the "All Rash" category included erythema in the single dose studies and rash in the repeat dose studies. In unblinded data in studies LAM100034 and LAM100036 combined, terms comprising the "All Rash" category included rash, rash generalized, rash papular, and rash pruritic.

Overview of Safety Analyses of This NDA Review

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

An integrated analysis of key safety data from LAM100034 and LAM100036, LAM100036 blinded subjects, single dose healthy volunteer studies (LAM102611, LAM10014, and LAM10005) and repeat dose healthy volunteer studies (LAM10017, LAM10005) was performed to support evidence of safety for the lamotrigine XR formulation. Supporting safety data from study LEP103944 are summarized directly from the LEP103944 complete study report (CSR).

The sponsor provided a tabular listing of all clinical studies providing safety data for this submission, source tables and figures for the integrated safety data, narratives for SAEs and AEs leading to study discontinuation, and a listing of post-marketing reports.

The analysis of safety focused specifically on AEs, drug exposure, clinical laboratory values and ECGs. All subjects who received at least one dose of study drug were analyzed for safety and summarized by study type. In the blinded subjects from the LAM100036 Double-Blind phase, only SAEs, deaths, and discontinuations due to AEs were analyzed.

Groupings of Studies for Safety Analyses
GSK integrated the safety findings from six of the eight studies included in the clinical development program for the lamotrigine XR formulation. LEP103944, an open-label, double conversion study to characterize the PK of lamotrigine when switching subjects with epilepsy on lamotrigine IR to lamotrigine XR formulation and vice versa, was not included in the combined summaries due to the short duration of treatment (2 weeks on lamotrigine XR) and study design compared to the other open-label studies. The safety data from healthy volunteers who received the XR formulation are summarized by single dose studies (LAM10005 Part A, LAM10014 and LAM102611) and repeat dose studies (LAM10005 Part B and LAM10017). LAM10007 and LAM10004 were exploratory pharmacokinetic studies which did not utilize the XR formulation, so the safety data are not included in this overview. Safety results from these studies are summarized in the individual LAM10007 and LAM10004 CSRs. In the clinical pharmacology studies, standard safety evaluations were performed prior to and following study participation and at frequent intervals during each study. These included recording of AEs, physical examination, measurement of vitals signs, electrocardiography and clinical laboratory testing (hematology, clinical chemistry, urinalysis and drugs of abuse screens).

The sponsor noted that to make valid comparisons from different study designs and patient populations, the following study groupings were summarized across studies:
• Healthy Volunteers, single dose: LAM102611, LAM10014, and LAM10005 (Part A). Although the designs are slightly different, all had pre-dose measurements and at least 1 post-dose measurement within 21 days of the last dose.
• Healthy Volunteers, repeat dose: LAM10017, LAM10005 (Part B). Although the duration of treatment was different between studies (LAM10017 dosed for 74 days and LAM10005 for 14 days in period 2) and assessments were not equally timed, all had pre-dose measurements and at least 1 post-dose measurement within 21 days of the last dose.

LAM100034 and LAM100036: Both studies are identical in study design with a double-blind, placebo controlled phase followed by an open-label Continuation Phase. Safety data for subjects exposed to lamotrigine XR during both the double-blind and Continuation Phase of LAM100034 were integrated and analyzed along with ONLY the safety data for subjects participating in the Continuation Phase of LAM100036.

• Subjects, Blinded: LAM100036 Double-blind phase. Since there will not be an interim report nor will the data be unblinded for the submission, it is appropriate to summarize the safety data here. The pivotal study (LAM100034) will be unblinded and reported separately.
• Subjects, LAM100034. All safety data generated by the placebo controlled phase of pivotal study LAM100034 will be summarized directly as provided in the individual CSR.
For study LAM10005, only the data for the 15-hour formulation were summarized as this was the release rate used in the pivotal study (LAM100034).

All analyses described herein were performed after all subjects had completed their last assessment and the databases had been cleaned and frozen per GSK SOPs. For ongoing studies, the data cut-off date was 28 June 2006.

All studies (with the exception of LAM100036 double-blind phase) were analyzed using the actual treatment assignments. The LAM100036 blinded data were summarized as a single group, regardless of actual randomization (i.e., subjects exposed to placebo and lamotrigine XR were summarized as a single group).

Integrated Safety Analyses
The primary objective of the integrated safety summaries was to provide across study summaries of AEs, clinical laboratory evaluations, ECGs and exposure data in order to completely characterize the experience of XR lamotrigine.
Secondary objectives were :

• Examination of AEs by subgroups (age, race, sex, average daily dose) and events of special interest (Rash)

• Examination of long-term exposure to lamotrigine XR
All subjects who received at least one dose of study drug were analyzed for safety and summarized by study type.

The sponsor noted that vital signs data were not integrated as part of this plan because of the lack of significant elevation or changes compared to the IR lamotrigine formulation. Additionally, quantitative clinical labs and ECGs were not included as part of the integrated analysis; only those values beyond the threshold of clinical concern were integrated. These analyses are more clearly interpretable in a placebo-controlled setting; therefore, we have referenced the data summarized in the individual study reports for LAM100034 and SCA104648 (for ECGs only) as the definitive analysis of this data.

Description of Safety Population
Selected safety data generated by clinical pharmacology studies and studies LAM100034 and LAM100036 were summarized to support the existing, extensive safety database for LAMICTAL derived from previous clinical studies and marketed use. The Safety Population in the integrated analysis consisted of all subjects who took at least one dose of XR lamotrigine.

The following subgroups were examined in the integrated analysis :
• Age (<16, 16-65, >65 years)
• Race
• Sex
• Background AED group (patient populations), defined as:
• VPA/DVS with an enzyme inducing AED (EIAED): the enzyme inducing AEDs are carbamazepine, phenytoin, phenobarbital, primidone, ethotoin, mephenytoin, and methylphenobarbital.
• VPA/DVS alone or with a non-EIAED: See above bullet for a list of EIAEDs.
• EIAED alone or with non-inducing/inhibiting AED: Subjects on EIAEDs alone (see first bullet) or in combination with a non-inducing/inhibiting AED (all other drugs except EIAEDs, VPA or DVS).
• All other regimens: Subjects who do not belong to any of the groups above will be classified here.

Reviewer Comment

There were some limitations in the scope of safety data reported in the original NDA submission and 4 Month Safety Update (4MSU) compared to the scope and completeness of data typically reported in NDAs. These limitations are noted here.

- The open label (OL) safety experience from the extension phase of study 34 is limited only to adverse events because clinical laboratory tests, vital signs, and ECGs were not collected in this phase.

- The TEAEs reported from the OL phases of studies 36 could include patients who had completed the study and others who had undergone treatment in this phase for various times. Considering that patients exposed to drug for a relatively short period would have had limited exposure time, they may not have had sufficient time to experience a TEAE that could have developed with longer exposure. Including such patients who may not have yet experienced a certain TEAE in the denominator (i.e. total # patients exposed) may lower the apparent frequency of the specific TEAE.

- The presentation of blinded safety results for the controlled phase of study 36 was not very helpful in assessing the safety of XR lamotrigine.

The following summarizes the status of patient data for ongoing studies at the time of the original NDA submission and 4MSU.

OL Study Phase LAM100034:

NDA cut-off of June 28, 2006 (29 patients out of study as completer or discontinued prematurely)
10 patients completed
19 patients withdrew prematurely

Adverse Event	5
Non-compliance	1
Lost to Follow-up	1
Did not meet eligibility criteria	5
Protocol violation	1
Subject decided to withdraw from study	3
Lack of efficacy	2
Other	1

120-day update cut-off of Oct 31, 2006 (75 patients out of study as completer or discontinued prematurely)
35 patients completed
40 patients withdrew prematurely

Adverse event	12
Non-compliance	3
Lost to follow-up	2
Did not meet eligibility criteria	5
Protocol violation	5
Subject decided to withdraw from study	7
Lack of efficacy	4
Other	2

OL Study Phase LAM100036:

NDA cut-off of June 28, 2006 (9 patients out of study as completer or discontinued prematurely)
6 patients completed

3 patients withdrew prematurely

Adverse event	1
Lost to follow-up	1
Other	1

120-day update cut-off of Oct 31, 2006 (21 patients out of study as completer or discontinued prematurely)

16 patients completed

5 patients withdrew prematurely

Adverse event	1
Non-compliance	1
Lost to follow-up	1
Subject decided to withdraw from study	1
Other	1

Study LAM30055 (XR lamotrigine for monotherapy:

No completions at either the NDA cut-off or the 4MSU

Reviewer Approach to Safety Review

This reviewer's review of the safety data focused on the randomized, double-blind, placebo-controlled study LAM0034 that was the only study providing unblinded, placebo-controlled safety data. Such data from this study are the main body of safety data presented in my review. Although I reviewed the safety data from the sponsor's integrated analyses, I have only presented data from these integrated analyses ONLY when I deemed that there were noteworthy data appropriate of presentation.

These integrated analyses combined lamotrigine-XR associated results from the placebo-controlled study phase of LAM100034 and from pen-label phases of LAM100034 and LAM1036 and also from studies for different treatment indications (LAM10034 – adjunctive treatment of partial epilepsy and LAM10036 –adjunctive treatment of primary generalized tonic-clonic-PGTC epilepsy). Although we occasionally review analyses of integrated safety results from controlled and open-label phases, and among different treatment indications, more frequently we focus on integrated safety analyses of pooled randomized, double-blind, controlled studies (that are at least generally similar in study design) and of pooled analyses of the same treatment indications.

7.1.1 Deaths

One death (sudden, unexpected death ultimately thought to be related to a complex partial seizure) occurred during study LAM100034 (Subject 62: LTG XR group). The event was not considered by the investigator to be related to study drug because the subject was randomized but never received a dose of study medication.

No deaths were reported in healthy volunteers in the clinical pharmacology studies. There were no deaths reported during study LEP103944 or ongoing study LAM100036 as of the safety data cut-off date of 28 June 2006.

Two deaths occurred in subjects receiving lamotrigine XR (Subject 1546 and 2152) during the Open-label Continuation Phase of study LAM100034 as of the cut-off date of 28 June 2006.

Narrative of Death for Patient # 2152
The subject's medical history included partial seizures since 1999, moderate myopia with partial atrophy of optic nerves, intracranial hypertension, hypoplasia of the uterus, and a suspected right ovarian cyst. A diagnosis of cryptogenic epilepsy was made on 13 March 2002 but was changed to symptomatic epilepsy after an MRI showed arachnoid cysts of middle cranial fossae bilaterally, cysts of maxilla and sphenoid bones, and mild internal and external hydrocephalus. This patient was unable work because of the frequency of her seizures.

The subject (from the Russian Federation) was enrolled in a blinded study (LAM100034) for the treatment of partial seizure and was randomized to receive lamotrigine XR during the blinded phase of this study. Concomitant medications included valproic acid and clonazepam. XR lamotrigine was started on 12.5 mg daily on 13 January 2006, and was titrated up to 200 mg daily on 03 March 2006.

During the baseline 8 weeks, the subject had a total of 8 seizures, all of which were secondarily generalized tonic-clonic (SGTC). During the 8 week escalation phase, the subject had a total of 5 SGTC seizures, the last of which occurred on 04-February-2006. The subject's participation in the trial had led to a decrease in seizures and improved seizure control and an increase in social adaptation. At the end of the blinded phase of the study, the investigator considered the subject to be markedly improved in comparison to baseline. Four blood samples were collected for pharmacokinetic assessment of lamotrigine from Subject 2152 while on the 200mg dose of LTG-XR. The subject had lamotrigine serum concentrations that were consistently high during the blinded phase of the study, but the subject was not noted to have symptoms of toxicity during this part of the study.

During the transition from the blinded phase to the open label phase, the subject's dose of LTG-XR was mistakenly doubled from 200mg/day to 400mg/day on 26-May-2006 to 02-June-2006. The subject noted toxicity with diplopia and vomiting from 29-May-2006 to 02-June-2006, **which resolved when the subject resumed the correct dose of 200mg/day**. Clinical data is available during the open label phase through the subject's last clinic visit on 13-July-2006. Neither the subject's seizure diary nor study drug were found after the subject's death (i.e. no records are available for 14-Jul-06 to 26-July-2006). The subject remained seizure-free from 05-February-2006 to 13-July-2006. Throughout the study for which records are available, the subject was noted to be 100% compliant without any deviations in study medication.

On (b) (6), approximately (b) (6) weeks after the first dose of investigational product, and (b) (6) weeks after the first dose of open-label lamotrigine in the continuation phase, the subject was found dead. The date of death was given as (b) (6).

The death was initially classified as sudden death, but this was changed after an autopsy, when the subject was diagnosed as having died from lamotrigine poisoning, despite not having symptoms of toxicity during the continuation phase, including the days before the subject's death.

An autopsy was performed on (b) (6). The forensic report stated that 'the examination revealed the agent lamotrigine in the blood, urine, the stomach contents, the liver and kidney. In the blood and urine no ethanol was identified. In the liver and kidney as well as in the contents of the stomach, no clonazepam, phenobarbital, barbital, barbamilum, ethaminal, cyclobarbital, morphine, codeine, trimeperidine (promedolum), cocaine, oxazepam, nitrazepam, diazepam, chlordiazepoxide, phenazepam, chlorpromazine (aminazin), diprazin, levomepromazine (tizertsin), trifluoperazine (triphthazine), thioproperazine (majeptil) or imizin was detected. The urine exam identified no opioids. Following this examination, the final diagnosis of the cause of death according to the autopsy conclusion from the Chief of Balashikha Office of Forensic Pathology was acute lamotrigine poisoning.

According to the subject's diaries, there was no evidence of suicidal ideation in the past. The investigator considered that there was a reasonable possibility that the acute lamotrigine poisoning may have been caused by the investigational product. The noted that The investigator indicated that the acute lamotrigine poisoning represented a possibly intentional lamotrigine overdose, although there was no evidence that the subject had overdosed with lamotrigine (e.g. no tablets were found by the subject's relatives). According to the chemical autopsy report no analysis of lamotrigine concentrations were performed. Qualitative assay of blood and serum showed the presence of lamotrigine, but clonazepam was not present (despite records showing that the subject had been treated with and was compliant with clonazepam 1mg tid).

The sponsor indicated that the final autopsy report can only be obtained through a court order.

GSK Assessment : The most likely diagnosis in this case is sudden unexpected death in epilepsy (SUDEP). The subject had a history of uncontrolled secondarily generalized tonic-clonic seizures. There was marked improvement in seizure control and function while the subject was treated with LTG-XR. The subject had no history of depression or suicidality/suicide attempts. While the post-mortem toxicology qualitatively identified lamotrigine being present, no quantitative analysis was performed on post-mortem samples to confirm lamotrigine poisoning. Additionally, clonazepam was not qualitatively identified in the post-mortem samples, raising the issue of accuracy of the analysis or whether the subject had self discontinued the clonazepam, leading to increased risk of withdrawal seizures/status epilepticus.

Reviewer Comment

- The history does not explicitly suggest an overdose of lamotrigine. The lamotrigine label notes that some cases of lamotrigine overdose (up to 15 mg) have been fatal. Although the autopsy revealed positive qualitative samples for lamotrigine in several tissues, it is difficult to know if this would not necessarily be expected in a patient chronically using lamotrigine. The absence of quantitative measurements of high lamotrigine

concentrations in these tissues makes it difficult to conclude that the patient may have died from acute lamotrigine poisoning. It seems possible that this patient may have died from sudden death, perhaps sudden death of epilepsy (SUDEP).

Narrative of Death for Patient # 1546
This 39-year-old female subject was enrolled in a blinded study for the treatment of partial seizure. The subject received oral investigational product from19 October 2005 to 28 February 2006 during the double-blind treatment phase, followed by open-label lamotrigine extended release 500mg daily.

The subject was receiving XR lamotrigine extended release during the double blinded phase beginning with 50 mg daily and titrating gradually up to 500 mg daily beginning on 07 December 2005.

During the afternoon of 24 June 2006, the subject developed seizures with vomiting (three to four episodes) and fever. Treatment with intramuscular diazepam 2 cc was administered. The subject was noted to have had a fever since 23 June 2006. The subject was conscious when she was hospitalized but later became unconscious. Treatment included ranitidine for gastritis and intravenous fluids. On (b) (6), the subject went into cardiac arrest. Cardiopulmonary resuscitation was administered along with adrenaline and atropine. The resuscitation was unsuccessful and the subject died. No autopsy was performed. During admission she was diagnosed with a generalized tonic-clonic seizure with aspiration pneumonia.

From follow-up information from 7/06, the cause of death was reported as severe generalized tonic-clonic seizure with aspiration. Concurrent medication included carbamazepine. The investigator considered that there was a possibility that the fatal generalized tonic-clinic seizure with aspiration was related to the investigational product. The investigator confirmed that the death was not related to lamotrigine.

Reviewer Comment

- There does not seem to be any reason to implicate lamotrigine as related to the cause of death in this patient.

7.1.2 Other Serious Adverse Events

Five (4%) subjects in the placebo group and 6 (5%) subjects in the LTG XR group reported treatment-emergent SAEs (Table 35). Two additional subjects in the LTG XR group (Subject 62 and Subject 1209) had SAEs which occurred prior to treatment with study drug.
No subject in the placebo group and 2 (2%) subjects in the LTG XR group had SAEs (pancreatitis, dizziness, headache, nystagmus) that were judged by the investigator to be reasonably attributable to study drug.

Four subjects were withdrawn as a result of a SAE (Subject 1809 in the placebo group, Subject 62 in the LTG XR group, Subject 1534 in the LTG XR group, and Subject 1840 in the LTG XR group). Two subjects had SAEs that had not resolved by the end of the Double-blind Phase of the study (Subject 581 in the placebo group and Subject 1534 in the LTG XR group).

No serious rashes were reported in study LAM100034.

Table 35 Serious Adverse Events (Safety Population: Placebo-Controlled Phase of LAM100034 and Controlled and Open-Label Phases of LAM100034 and Open-Label Phase of LAM100036)

Adverse Event	Number (%) of Subjects		
	LAM100034 Double-Blind Treatment Phase		LAM100034 and LAM100036 Combined
	Placebo N=121	LTG XR N=118	LTG XR N=311
Any Event	5 (4)	6 (5)	13 (4)
Nystagmus	0	1 (<1)	2 (<1)
Ankle fracture	0	0	1 (<1)
Intentional overdose	0	1 (<1)	1 (<1)
Tibia fracture	0	1 (<1)	1 (<1)
Complex partial seizures	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)
Dizziness	0	1 (<1)	1 (<1)
Grand mal convulsion	0	0	1 (<1)
Headache	0	1 (<1)	1 (<1)
Partial seizures	0	1 (<1)	1 (<1)
Status epilepticus	0	0	1 (<1)
Abdominal pain	0	0	1 (<1)
Gastritis	0	0	1 (<1)
Nausea	0	0	1 (<1)
Pancreatitis	0	1 (<1)	1 (<1)
Vomiting	1 (<1)	0	1 (<1)
Gastroenteritis viral	0	0	1 (<1)
Pneumonia viral	0	0	1 (<1)
Pyelonephritis acute	0	0	1 (<1)
Myocardial infarction	0	1 (<1)	1 (<1)
Sudden death	0	0	1 (<1)
Dehydration	0	1 (<1)	1 (<1)
Diabetic ketoacidosis	0	1 (<1)	1 (<1)
Aspiration	0	0	1 (<1)
Malignant Hypertension	0	0	1 (<1)
Radius fracture	1 (<1)	0	0
Drop attacks	1 (<1)	0	0
Urosepsis	1 (<1)	0	0
Diabetes mellitus	1 (<1)	0	0
Sepsis	1 (<1)	0	0
Urinary tract infection	1 (<1)	0	0
Uterine leiomyoma	1 (<1)	0	0
Urinary retention	1 (<1)	0	0
Hypokalaemia	1 (<1)	0	0
Hypomagnesaemia	1 (<1)	0	0
Cough	1 (<1)	0	0

Data Source: Table 5.50; LAM100034 CSR, Table 8.16

Reviewer Comment

- No specific SAE in the controlled study phase occurred more than once in any patient in either treatment group.

- With the exception of nystagmus, that occurred on 2 occasions, no other SAEs occurred more than once in the combined, integrated analyses.

- There did not seem to be any SAEs that were a cause for concern with XR lamotrigine treatment.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See section 7.1.3.2

7.1.3.2 Adverse events associated with dropouts

Adverse events leading to discontinuation in pivotal clinical study LAM100034 are summarized in (Table 36). Adverse events leading to withdrawal of study drug were reported for 2 (2%) subjects in the placebo group and 11 (9%) subjects in the lamotrigine XR group. Subjects may have been discontinued for more than one AE.

Of the 311 unique subjects exposed to lamotrigine XR in either controlled or open-label phase of LAM100034 and open-label phase of LAM100036 combined, 16 (5%) subjects were withdrawn due to an AE (Table 36). The most common AE leading to withdrawal of lamotrigine XR was dizziness (2%). Two subjects in the lamotrigine XR group in LAM100034 (Subject 1534: pancreatitis; Subject 1840: dizziness, headache, and nystagmus) were discontinued due to a treatment-emergent SAE during the Double-Blind Treatment Phase. Three subjects in LAM100034 (Subject 1546: grand mal convulsion and aspiration, fatal SAEs; Subject 2152: sudden death; Subject 411: status epilepticus) were discontinued due to a SAE during the Open-label Continuation/Extension Phase.

Table 36 Adverse Events Leading to Premature Discontinuation (Safety Population: Studies LAM100034 and LAM100036- Combined)

Adverse Event	Number (%) of Subjects		
	LAM100034 Double-Blind Treatment Phase		LAM100034 and LAM100036 Combined
	Placebo N=121	LTG XR N=118	LTG XR N=311
Any Event	2 (2)	11 (9)	16 (5)
Dizziness	0	4 (3)	5 (2)
Nausea	0	3 (3)	3 (<1)
Headache	1 (<1)	2 (2)	2 (<1)
Coordination Abnormal	0	2 (2)	2 (<1)
Nystagmus	0	2 (2)	2 (<1)
Asthenia	0	2 (2)	2 (<1)
Vertigo	0	1 (<1)	2 (<1)
All Rash[a,b]	0	1 (<1)	2 (<1)
Grand mal convulsion	0	0	1 (<1)
Intention tremor	0	1 (<1)	1 (<1)
Status epilepticus	0	0	1 (<1)
Tremor	0	1 (<1)	1 (<1)
Gait disturbance	0	1 (<1)	1 (<1)
Malaise	0	0	1 (<1)
Sudden death	0	0	1 (<1)
Pancreatitis	0	1 (<1)	1 (<1)
Stomach discomfort	0	1 (<1)	1 (<1)
Anxiety	0	1 (<1)	1 (<1)
Depression	0	1 (<1)	1 (<1)
Psychomotor retardation	0	1 (<1)	1 (<1)
Diplopia	0	1 (<1)	1 (<1)
Aspiration	0	0	1 (<1)
Hot flush	0	1 (<1)	1 (<1)
Drop attacks	1 (<1)	0	0
Oral pruritus	1 (<1)	0	0
Vomiting	1 (<1)	0	0
Pruritus	1 (<1)	0	0
Cough	1 (<1)	0	0

Data Source: Table 5.62; LAM100034 CSR, Table 8.19
a. In LAM100034, terms comprising the "All Rash" category included rash generalized.
b. In LAM100034 and LAM100036 combined, terms comprising the "All Rash" category included rash and rash generalised.

Three subjects in a repeat-dose/multidose clinical pharmacology study (LAM10017) were withdrawn due to rash; two of mild and one of moderate intensity, which lasted between 5 and 11 days.

Reviewer Comment

- The most common (≥ 2 patients) TEAEs causing study discontinuation were TEAEs that are shown to be associated with lamotrigine treatment in the label by occurring more frequently in lamotrigine treatment group than with placebo.

7.1.3.3 Other significant adverse events

TEAEs of Special Interest (Rash)

Rash is an AE of special interest in the lamotrigine IR clinical development program. In the lamotrigine XR clinical pharmacology studies in healthy volunteer studies, terms comprising the "All Rash" category included erythema in the single dose studies and rash in the repeat dose studies. In unblinded data in studies LAM100034 and LAM100036 combined, terms comprising the "All Rash" category included rash, rash generalized, rash papular, and rash pruritic. In current LAMICTAL product labeling, serious rash is defined as rash associated with hospitalization and the discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis. There were no cases of serious rash in the lamotrigine XR clinical development program. There were no cases of Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Clinical Pharmacology Studies

Table 37 summarizes the overall incidence of rash, rash attributable to study drug, rash leading to study discontinuation, rash reported as SAEs, and serious rash in clinical pharmacology studies in healthy volunteers. One (< 1%) subject receiving lamotrigine XR had an AE of rash in the single dose studies. This was mild, considered drug-related, and recovered in 2h.

Four (10%) subjects receiving lamotrigine XR in the repeat dose studies had an AE of rash, which in three cases led to the subject's withdrawal. The rashes started, on average, 9.5 days after the start of dosing and lasted, on average, 9.5 days; three were mild and one moderate. Two rashes were considered drug-related, and two unrelated; all resolved.

The incidence of rash among all healthy volunteers subjects exposed to lamotrigine XR was similar to the incidence of rash among adults exposed to lamotrigine IR. In LAM10017 there were five rashes; two in lamotrigine IR group and three in lamotrigine XR group.

None of the lamotrigine-treated subjects had a serious rash in the clinical pharmacology program, defined by GSK as any rash that was associated with hospitalization and the discontinuation of lamotrigine, or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Table 37 Incidence of Rash (Safety Population: Clinical Pharmacology Studies)

Adverse Event Category	Number (%) of Subjects	
	Single Dose N=184	Repeat Dose N=41
All Rash[a]	1 (<1)	4 (10)
All Rash Attributable to Study Drug	1 (<1)	2 (5)
All Rash Leading to Study Discontinuation	0	3 (7)
All Rash Considered to be SAEs	0	0
Serious Rash[b]	0	0

Data Source: Table 5.22, Table 5.23, Table 5.32, Table 5.33, Table 5.48, Table 5.49, Table 5.60 and Table 5.61

a. In healthy volunteer studies, terms comprising the "All Rash" category included erythema in the single dose studies and rash in the repeat dose studies.

b. In current LAMICTAL product labeling, serious rash is defined as a rash associated with the use of LAMICTAL that requires hospitalization and discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Clinical Studies

In pivotal study LAM100034, rash was reported by 1 (< 1%) subject in the placebo group and 2 (2%) subjects in the lamotrigine XR group. There were no reports of serious rash in either treatment group. Rash was considered to be reasonably attributable to study drug for no subject in the placebo group and for 1 (< 1%) subject in the lamotrigine XR group. No subject in the placebo group and 1 (< 1%) subject in the lamotrigine XR group was discontinued due to rash.

Table 38 summarizes the overall incidence of rash, rash attributable to study drug, rash leading to study discontinuation, rash reported as SAEs, and serious rash in studies LAM100034 and LAM100036 combined. In studies LAM100034 and LAM100036 combined, the overall incidence of treatment-emergent rash on lamotrigine XR in unblinded subjects was 4% (13 subjects). One additional subject experienced rash prior to receiving study drug. There were no reports of serious rash. Rash was considered to be reasonably attributable to study drug for 6 (2%) subjects receiving lamotrigine XR and two (<1%) subjects receiving lamotrigine XR were discontinued due to rash.

A summary of the characteristics of rash reported in unblinded subjects in LAM100034 and LAM100036 combined is provided in Table 39. All cases of rash reported in unblinded subjects in LAM100034 and LAM100036 combined were mild or moderate in intensity with the exception of one subject that experienced three rash-related AEs of severe intensity. The onset and duration of the first occurrence of rash are summarized for unblinded subjects in LAM100034 and LAM100036 combined in Table 40. The time to first rash is presented graphically in Figure 8. The rashes started, on average, 53.5 days after the start of dosing and lasted, on average, 17.4 days.

The incidence of rash for lamotrigine XR in pivotal study LAM100034 (2%) and studies LAM100034 and LAM100036 combined (4%) was lower than previously reported in earlier controlled epilepsy studies of lamotrigine IR as adjunctive therapy (10%) in the lamotrigine label. Although no serious rashes were reported in this program, the number of subjects may be too small given the rate noted with lamotrigine IR (0.3%).

Table 38 Incidence of Rash (Safety Population: Studies LAM100034 and LAM100036- Combined)

Adverse Event Category	Number (%) of Subjects		
	LAM100034 Double-Blind Treatment Phase		LAM100034 and LAM100036 Combined
	Placebo N=121	LTG XR N=118	LTG XR N=311
All Rash[a,b]	1 (<1)	2 (2)	13 (4)
All Rash Attributable to Study Drug	0	1 (<1)	6 (2)
All Rash Leading to Study Discontinuation	0	1 (<1)	2 (<1)
All Rash Considered to be SAEs	0	0	0
Serious Rash[c]	0	0	0

Data Source: Table 5.24, Table 5.34, Table 5.50, Table 5.62; LAM100034 CSR, Table 8.5, Table 8.15, Table 8.16 and Table 8.19

a. In LAM100034, terms comprising the "All Rash" category included rash and rash generalized.
b. In LAM100034 and LAM100036 combined, terms comprising the "All Rash" category included rash, rash generalised, rash papular, and rash pruritic.
c. In current LAMICTAL product labeling, serious rash is defined as a rash associated with the use of LAMICTAL that requires hospitalization and discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis.

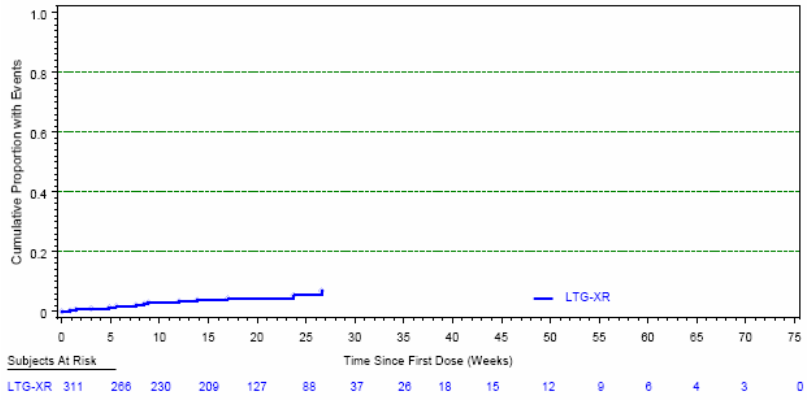
Table 39 Summary of Characteristics of Rash in Unblinded Patients (Studies LAM100034 and LAM100036- Combined)

	LTG-XR (N=311)
Number of Subjects with Events	14 (5%)
Number of Events	17
Event Characteristics	
N	17 (5%)
Serious	0
Drug-related	9 (3%)
Leading to Withdrawal	4 (1%)
Severe	3 (<1%)
Number of occurrences	
N	14 (5%)
One	12 (4%)
Two	1 (<1%)
Three or more	1 (<1%)
Outcome	
N	17 (5%)
Recovered/resolved	12 (4%)
Recovering/resolving	3 (<1%)
Not recovered/not resolved	1 (<1%)
Recovered/resolved with sequelae	1 (<1%)
Fatal	0
Frequency	
N	17 (5%)
Single episode	15 (5%)
Intermittent	2 (<1%)
Missing	0
Maximum Intensity	
N	17 (5%)
Mild	5 (2%)
Moderate	9 (3%)
Severe	3 (<1%)
Action Taken	
N	17 (5%)
Investigational product withdrawn	4 (1%)
Dose reduced	1 (<1%)
Dose increased	0
Dose not changed	10 (3%)
Dose interrupted	1 (<1%)
Not applicable	1 (<1%)

Table 40 Summary of Onset and Duration of the First Occurrence of Rash in Unblinded Patients(Studies LAM100034 and LAM100036- Combined)

	LTG-XR (N=311)
Number of Subjects Experiencing All Rash	14 (100%)
Time of onset, days	
N	14
1 - 14	3 (21%)
15 - 28	1 (7%)
>28	10 (71%)
Mean	53.5
SD	57.57
Median	46
Min.	-57
Max.	196
Duration, days	
N	10
1 - 5	6 (43%)
6 - 10	3 (21%)
>10	5 (36%)
Mean	17.4
SD	17.16
Median	11
Min.	1
Max.	57

Figure 8 **Time to First Rash in Unblinded Patients (Relative to # of Patients in Combined Analyses of Study LAM100034 and LAM100036))**



7.1.4 Other Search Strategies

Additional analyses were requested from the sponsor by this reviewer. These analyses (

Table 41) assessed the frequency (incidence, # of TEAEs, rate of TEAEs) of TEAEs occurring in the titration phase, the maintenance phase, the whole study phase of the randomized, double-blind, placebo-controlled study (LAM100034) and having their onset in the titration phase and "persisting" into the maintenance phase. TEAEs were to be presented not only according to system organ class (SOC) and preferred term (PT) classification/coding, but also the according to higher level group term (HLGT) and higher level term (HLT) and also according to various dose ranges (and "any" dose) based upon the time/phase of onset of the TEAE. Calculation of treatment effect (lamotrigine % incidence – placebo % incidence) was an additional analysis requested. Similar analyses (Table 42) of TEAE rates and treatment effect for TEAE rates were also requested.

Subgroup analyses of the above requested analyses were also requested based upon each type of class of concomitant AED : enzyme-inducing AED (EIAED; e.g. phenytoin or phenobarbital), nonEI/"neutral" AED (e.g. topiramate, levitiracetam), valproic acid (VPA), and "any" combination of concomitant AED. Whereas an EIAED can decrease plasma lamotrigine levels, VPA can increase plasma lamotrigine levels.

Similar analyses were requested for open-label study LEP103944 that assessed conversion to lamotrigine XR treatment for 2 weeks in patients treated with lamotrigine IR and who had prospectively been observed for 2 weeks, and who were switched back to lamotrigine IR and followed for 1 week after treatment with lamotrigine XR for 2 weeks.

Table 41 TEAE Treatment Effect Incidence* (TE % = XR Lamotrigine % - Placebo %) in Titration (7 weeks) and/or Maintenance (12 weeks) Period/Phase of Study LAM100034

TEAE with Onset in Titration Period		TEAE with Onset in Maintenance Period		TEAE with Onset in Titration and/or Maintenance Period	
TEAE	TE %	TEAE	TE %	TEAE	TE %
Dizziness	4	Dizziness	9	Dizziness (DR)	13
Diarrhea	4	Tremor	5	Asthenic conditions (asthenia, fatigue, malaise)	5
Vertigo	3	Asthenic conditions (asthenia, fatigue, malaise)	4	Depression	3
Nausea	3	Vomiting	2	Vertigo	3
Somnolence	3	Vertigo	2	Nausea	3
Diplopia	3	Nystagmus	2	Diplopia	3
Hot flush	3	Depression	2	Coordination abnormal(DR)	3
Pharyngolaryngeal pain	3	Balance Disorder	2	Tremor	3
Depression	2	Migraine	2	Diarrhea	3
Dry mouth	2	Abdominal pain	2	Migraine	3
Anxiety	2			Hot flush	3
Coordination abnormal	2			Vomiting	2
Asthenic conditions (asthenia, fatigue, malaise)	2			Anxiety	2
Migraine	2			Gait disturbance	2
Pain in extremity	2			Anorexia	2
Myalgia	2			Nystagmus (DR)	2
				Headache	2
				Myalgia	2
				Ischemic coronary artery disorder	2
				Abdominal pain	2
				Stomach Discomfort	2
				Chest discomfort	2
				Pharyngolaryngeal pain	2
				Sinus congestion	2

* Presented for Treatment Effect Incidence (TE % = XR Lamotrigine % -Placebo %) $\geq$ **2%** (rounded off)
DR = Dose- Related

Table 42 TEAE Treatment Effect Rate* (TE Rate = XR Lamotrigine Rate – Placebo Rate) in Titration (7 weeks) and/or Maintenance (12 weeks) Period/Phase of Study LAM100034

TEAE with Onset in Titration Period		TEAE with Onset in Maintenance Period		TEAE with Onset in Titration and/or Maintenance Period	
TEAE	TE Rate	TEAE	TE Rate	TEAE	TE Rate
Depression	0.193	Dizziness	0.161	Depression	0.194
Nausea	0.181	Vertigo	0.159	Vertigo	0.116
Diarrhea	0.138	Vomiting	0.103	Nausea	0.097
Dizziness	0.060	Back pain	0.098	Dizziness	0.074
Somnolence	0.059	Tremor	0.056		
Hot flush	0.050				

* Rate calculated based upon # TEAEs/12 Weeks
Rate presented only for Treatment Effect Rate* (TE = XR Lamotrigine rate -Placebo rate) **≥ 0.05**

Reviewer Comment

- It is important to be aware of the criterion for including TEAEs in the results shown in
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- Table 41 before I compare and contrast these results of TEAEs associated with XR lamotrigine treatment with those in the IR lamotrigine label. To be included in this table, TEAEs associated with XR lamotrigine had to occur at an incidence frequency of ≥ 2 % (after rounding off) higher than placebo treatment.

- The analyses of the incidence of TEAEs in the titration phase, in the maintenance phase, or in any phase during the whole study (shown in
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- Table 41) identified many TEAEs that occurred more frequently with XR lamotrigine treatment than with placebo treatment during adjunctive treatment of adults with partial epilepsy. Not surprisingly, most of these TEAEs are also recognized to occur more frequently with IR lamotrigine treatment) than with placebo treatment (as per the label).

  Of interest, there were many TEAEs in

  Table 41 that are not in the label table of TEAEs occurring more frequently (at least ≥ 2 %) with IR lamotrigine treatment (than placebo) for adjunctive treatment of adult partial epilepsy. Technically, these TEAEs seemed unique to XR treatment of adults with partial epilepsy. These other TEAEs include. vertigo, nystagmus, hot flush, pharygnolaryngeal pain, migraine, headache, dry mouth, asthenic conditions (asthenia, fatigue, malaise), balance

disorder, myalgia, pain in extremity, ischemic coronary artery disorder, chest discomfort, stomach discomfort, and sinus congestion. However, a few of these are reported in the label as occurring more frequently with IR lamotrigine than with placebo for other indications and/or populations. For example, asthenia, vertigo, and gait disturbance were observed in the label table for treatment of pediatric partial epilepsy and dry mouth was observed in the table for treatment of bipolar adults. It is also relevant to note that the label tables of TEAEs occurring during treatment of partial seizures of adults as monotherapy and bipolar treatment of adults show only TEAEs when the frequency of IR lamotrigine was $\geq$ 5 % (and greater than the control). Thus, it is possible that some of these TEAEs might have been shown if a lower criterion for presentation was used.

"Unique" TEAEs (i.e. ? only occurring with XR lamotrigine) that do not appear in the many label tables of TEAE results for randomized, controlled with IR lamotrigine include nystagmus, hot flush, pharygnolaryngeal pain, migraine, headache, balance disorder, myalgia, pain in extremity, ischemic coronary artery disorder, chest discomfort, stomach discomfort, and sinus congestion. Although most of these TEAEs were 2 % more frequent than placebo, some TEAEs (hot flush, migraine, pharygnolaryngeal pain) were 3 % more frequent than placebo.

Of additional interest, a few of these "unique" XR TEAEs were a cause of study discontinuation and/or an SAE. Hot flush, nystagmus, and headache caused rare patients to discontinue from the controlled phase of study 34 (nystagmus, N=2; hot flush, N=1; headache, N=2 and 1 placebo also discontinued for headache). Two patients experienced nystagmus as an SAE (one in the controlled phase, and another in an OL treatment phase). One patient experienced headache as an SAE in the controlled phase.

It is somewhat difficult to believe or think that these TEAEs are really unique to XR lamotrigine and not also associated with IR treatment. Furthermore, although a preferred terms such as "stomach discomfort" does not appear in any lamotrigine label tables, these tables do described abdominal pain and dyspepsia. It is not clear if there are real distinction between these terms. Ultimately, the question is raised, whether these TEAEs are truly associated and caused by lamotrigine treatment? If so, a further question is raised as to whether many, if not all of these TEAEs, may occur with IR lamotrigine treatment but did not appear in the tables because of different TEAE coding or may actually occur but were not observed as occurring more frequently than control in the controlled clinical studies described in the IR lamotrigine label. Regardless, none of these TEAEs seem to clearly rise to a level of safety concern that would preclude approval of the XR formulation.

- These analyses suggested that some TEAEs associated with XR treatment occur predominantly in the titration phase (e.g. diarrhea, nausea) and others predominantly occur in the maintenance phase (e.g. tremor, vertigo, nystagmus, balance disorder, abdominal pain). Many other TEAEs shown in
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- Table 41 but not specifically mentioned here were also observed as more frequent for occurring at any time during the whole controlled study period.

- Some TEAEs developing in the titration phase persisted (≥ 7 days) into the maintenance phase. The frequency (treatment effect = XR lamotrigine % - Placebo %) for these "persistent" TEAEs was notable for dizziness (6%), somnolence (3%), dry mouth (2%), and hot flush (2%).

- Among the many TEAEs shown in
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- Table 41, only a few appear to be dose-related based upon arbitrary dose ranges (< 300 mg/d, 300-< 500 mg/d, ≥ 500 mg/d) that I had asked the sponsor to analyze these data. These TEAEs included dizziness, coordination abnormal, and nystagmus during the whole study period.

  That most TEAEs did not suggest any dose-relationship is not surprising. Patients in each treatment (XR lamotrigine or placebo) were assigned to a target XR dose based upon concomitant AED class/group/type (i.e. any VPA = target 200 mg/d; any EIAED = target 500 mg/d; "neutral" AED not significantly altering lamotrigine levels and no VPA or EIAED = 300 mg/d) because previous experience with IR lamotrigine had suggested that the plasma levels in each of these groupings would be relatively similar. Indeed, the "conversion" study LEP103944 showed that the exposure (i.e. AUC) among all three concomitant AED groups receiving the XR formulation was relatively similar (mean AUC of each group ranging from ~ 80 % of IR lamotrigine level for EIAED group to ~ 100 % of IR lamotrigine level for "neutral" AED group) despite receiving different total daily doses. Considering that achieved plasma lamotrigine levels with each concomitant AED group (that might or might not increase or decrease lamotrigine levels) would be relatively similar despite receiving different targeted total daily doses, one would not necessarily expect that one would see dose-related TEAEs based upon total daily dose of XR lamotrigine.

  Regardless that most of these impressions or conclusions were drawn from OL "conversion" study LEP103944, I have not been able to identify specific analyses (by the sponsor nor in the Clinical Pharmacology review) showing the actual population PK results of solely patients randomized to each of the 3 concomitant AED groupings in controlled study 34 during the maintenance phase at weeks 11, 15, and 19. Mean results of each group at each timepoint and mean overall maintenance results of all patents in each concomitant AED grouping would seem to be of interest, particularly to compare how the patients in the controlled efficacy/safety study compared to results derived predominantly from the more comprehensive PK results and analyses of patients in the OL "conversion" study LEP103944.

- These analyses did not identify any unique TEAEs that had not be suggested as associated with XR treatment in the sponsor's analyses of the whole study period. The main information

identified with these incidence analyses was the TEAEs predominantly developing in the titration or maintenance phases.

- These analyses were assessed as to determine the occurrence of "frequent" recurrent TEAEs. The number of unique individuals with specific TEAEs was surveyed relative to the total number of specific TEAEs in each analysis to determine what TEAEs occurred in at least 2 individuals and had a ratio of $\geq$ 2.0 for total # events/total # unique patients with the TEAE in the "any" dose XR lamotrigine dose group.. This ratio was then compared to the respective ration in the placebo group. A few TEAEs that showed a ratio of $\geq$ 2.0 and had a ratio substantially greater than that of placebo are worthy of mention.

  In the titration phase, 5 XR lamotrigine-treated patients experienced 13 TEAEs of nausea (ratio=2.6) compared to one placebo patient with one TEAE of nausea (ratio=1.0). In addition, 14 XR lamotrigine-treated patients experienced 30 TEAEs of headache (ratio=2.14) compared to 14 placebo patients with 17 TEAEs of headache (ratio=1.31). During the whole study period, 4 XR lamotrigine-treated patients experienced 30 TEAEs of vertigo (ratio=5.0) compared to no placebo patients with vertigo (ratio=0). In this same period, 7 XR lamotrigine-treated patients experienced 15 of nausea (ratio=2.14) compared to 3 placebo patients with 3 TEAEs of nausea (ratio=1.0).

  These analyses suggested that there can be a significant recurrence of nausea and headache in the titration period and also a significant recurrence of vertigo and nausea at any time throughout the whole treatment period.

- The analyses of rate of TEAEs (# TEAEs/12 weeks) included unique individuals with a single specific TEAE and unique individuals with recurrent specific TEAEs (Table 42). Overall, these analyses did not suggest an association of XR lamotrigine treatment about the development of any TEAE than had been suggested by the incidence analyses. The only TEAE identified in this analysis that had not been suggested in the incidence analyses was back pain that occurred with a notable rate (vs placebo) in the maintenance period.

  In general, the hierarchy of the frequency of TEAEs according to the incidence analyses was similar. There was, however, one notable exception, depression was the most frequent TEAE in the titration rate analyses (Table 42) but was not such a prominent TEAE in the incidence analysis during this same phase (

  Table 41).

  In the analysis of the rates of "persistent" TEAEs, dizziness (0.097) was the only notable TEAE occurring more frequently than the placebo rate.

- Some of these findings generated through these exploratory analyses may be worthy of description in the label.

- There were no clear or unique safety findings that appeared as result of these analyses based upon concomitant AED group compared to the findings observed from analyzing the data according to the 3 dose ranges (e.g. < 300 mg/d, 300-<500 mg/d, and ≥500 mg/d). This is not very surprising considering that concomitant VPA use was typically associated with a total daily dose of < 300 mg/d, concomitant "neutral" AED use was typically associated with a total daily dose of 300-<500 mg/d, and concomitant EIAED use was typically associated with a total daily dose of ≥500 mg/d.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

No special approach/attention was used to elicit TEAEs in the development program.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Reviewer Comment

- Overall, the coding of verbatim terms (VTs) to preferred terms (PTs) appeared to be reasonable for most TEAEs based upon my review of the coding of VTs to PTs.

7.1.5.3 Incidence of common adverse events

A summary of the TEAEs in ≥ 2% of the LTG XR group and TEAEs that occurred more frequently on LTG XR than placebo in study 34 is provided in Table 43. Table 44 shows TEAEs in ≥ 2% of LTG XR in the DBP of study 34 and the open-label, extension phases of studies 34 and 36.

The sponsor noted that most of the TEAEs were mild or moderate in intensity.

Table 43 **TEAEs in ≥ 2% of Subjects in the LTG XR and AEs Occurring More Frequently in the LTG XR Group Than in the Placebo Group (Safety Population: Study LAM100034)**

Preferred Term	Number (%) of Subjects	
	PBO N=121	LTG XR N=118
Any Event	75 (62)	81 (69)
Ear and Labyrinth Disorders		
Vertigo	0	4 (3)
Eye Disorders		
Vision Blurred	3 (2)	4 (3)
Diplopia	0	4 (3)
Gastrointestinal Disorders		
Diarrhea	5 (4)	8 (7)
Nausea	3 (2)	8 (7)
Vomiting	2 (2)	5 (4)
Constipation	1 (<1)	4 (3)
Dry Mouth	2 (2)	3 (3)
Abdominal Pain	0	2 (2)
Stomach Discomfort	0	2 (2)
General Disorders and Administration Site Conditions		
Asthenia	3 (2)	6 (5)
Fatigue	3 (2)	4 (3)
Chest Pain	1 (<1)	2 (2)
Chest Discomfort	0	2 (2)
Gait Disturbance	0	2 (2)
Pain	1 (<1)	2 (2)
Infections and Infestations System		
Sinusitis	1 (<1)	3 (3)
Injury, Poisoning and Procedural Complications		
Contusion	1 (<1)	2 (2)
Investigations		
Weight Increased	1 (<1)	2 (2)
Metabolism and Nutrition Disorders		
Anorexia	0	2 (2)
Musculoskeletal and Connective Tissue Disorders		
Myalgia	0	2 (2)
Shoulder Pain	0	2 (2)
Nervous System		
Dizziness	6 (5)	21 (18)
Headache	18 (15)	20 (17)
Somnolence	5 (4)	8 (7)
Tremor	1 (<1)	6 (5)
Coordination Abnormal	1 (<1)	4 (3)
Nystagmus	1 (<1)	3 (3)
Migraine	0	3 (3)
Intention Tremor	1 (<1)	2 (2)
Balance Disorder	0	2 (2)
Psychiatric Disorders		
Depression	1 (<1)	5 (4)
Anxiety	0	2 (2)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal Pain	2 (2)	4 (3)
Epistaxis	1 (<1)	2 (2)
Sinus Congestion	0	2 (2)
Skin and Subcutaneous Tissue Disorders		
All Rash[1]	1 (<1)	2 (2)
Vascular Disorders		
Hot Flush	0	3 (3)

Data Source: Table 8.5 and Table 8.8

1. Terms comprising 'All Rash' category: Rash, Rash generalized

Table 44 TEAEs in ≥ 2% Patients (N=311) Treated with LTG XR in Placebo-Controlled Phase of Study LAM100034 AND Open-Label Continuation Phases of Studies LAM100034 and 100036 (Completers and Ongoing)

System Organ Class and Preferred Term	Number (%) of Patients
Any Event	156 (51 %)
Ear and Labyrinth Disorders	
Vertigo	8 (3 %)
Eye Disorders	
Diplopia	8 (3 %)
Vision Blurred	7 (2 %)
Gastrointestinal Disorders	
Nausea	21 (7 %)
Vomiting	14 (5 %)
Diarrhea	10 (3 %)
Constipation	5 (2 %)
Dry Mouth	5 (2 %)
General Disorders and Administration Site Conditions	
Fatigue	8 (3 %)
Asthenia	7 (2 %)
Infections and Infestations	
Nasopharyngitis	7 (2 %)
Nervous System Disorders	
Headache	41 (13 %)
Dizziness	39 (13 %)
Somnolence	13 (4 %)
Tremor	12 (4 %)
Coordination Abnormal	8 (3 %)
Balance Disorder	6 (2 %)
Pharyngolaryngeal Pain	6 (2 %)
Psychiatric Disorders	
Insomnia	11 (4 %)
Depression	6 (2 %)
Skin Disorders and Subcutaneous Tissue Disorders	
Rash (All)	13 (4 %)

Data Source : Integrated Analysis Table 5.24

Reviewer Comment

- Most of these TEAEs (Table 43) that were observed more frequently than placebo in the controlled study phase are TEAEs similarly observed as occurring more frequently with IR lamotrigine treatment than with placebo treatment in the lamotrigine label for the various controlled trial descriptions of TEAEs.

- My comments made in section 7.1.4 about the types of TEAEs observed (relative to the lamotrigine label) in the controlled phase of study 34 (derived from additional exploratory analyses of TEAEs) are also relevant here.

7.1.5.4 Common adverse event tables

Table 45 Most Common TEAEs (≥ 5% in Any Treatment Group) (Safety Population: Studies LAM100034 and LAM100036-Combined)

Adverse Event	Number (%) of Subjects		
	LAM100034 Double-Blind Treatment Phase		LAM100034 and LAM100036 Combined
	Placebo N=121	LTG XR N=118	LTG XR N=311
Any Event	75 (62)	81 (69)	158 (51)
Headache	18 (15)	20 (17)	41 (13)
Dizziness	6 (5)	21 (18)	39 (13)
Nausea	3 (2)	8 (7)	21 (7)
Vomiting	2 (2)	5 (4)	14 (5)
Somnolence	5 (4)	8 (7)	13 (4)
Diarrhea	5 (4)	8 (7)	10 (3)
Tremor	1 (<1)	6 (5)	12 (4)
Asthenia	3 (2)	6 (5)	7 (2)
Insomnia	7 (6)	4 (3)	11 (4)
Nasopharyngitis	13 (11)	3 (3)	7 (2)

Data Source: Table 5.24, Table 5.31; LAM100034 CSR, Table 8.5

Reviewer Comment

- The most common TEAEs associated with lamotrigine XR treatment were similar to TEAEs described in the lamotrigine IR label as a whole and occurring more frequently than with placebo treatment. However, Table 45 shown above presented the "most common" TEAEs based upon a ≥ 5 % incidence of TEAEs in either treatment group. I believe that a better index of the "most common" TEAEs is to assess their frequency by calculating the treatment effect (XR lamotrigine % - Placebo %) and correcting/adjusting for the placebo incidence.

  The treatment effect for the "most common" TEAEs shown in my

  Table 41 indicated that they included (in descending order of frequency) dizziness, asthenic conditions, depression, vertigo, nausea, diplopia, coordination abnormal, tremor, diarrhea, migraine, and hot flush. In comparison, the "most common" TEAEs for IR lamotrigine (based upon the descending treatment effect frequency for adjunctive treatment of adult partial epilepsy in the label) were dizziness, diplopia, ataxia, blurred

vision, headache, nausea, somnolence, rash, vomiting, and rhinitis. Thus, dizziness, asthenia, nausea, diplopia, and somnolence were shared in both lists for each formulation.

Generally, the treatment effect frequency was numerically quite different for XR vs the IR formulation, with higher frequencies typically occurring with IR treatment. However, it is difficult to know whether these quantitative differences are related to the formulation's effect per se or possibly to the populations studied. For example, almost two-thirds of the patients treated with XR lamotrigine were studied in foreign sites but approximately three-fourths of the patients in the adjunctive adult partial epilepsy controlled trials were studied in U.S. sites. In general, the frequency of drug associated TEAEs in controlled trials appears to be higher (often substantially higher) in the U.S. than in foreign sites, especially sites outside of Canada and Western Europe. Of potential relevance here, the majority (~ 55 %) of the patients in study 34 was studied in foreign sites outside of Canada and Western Europe.

7.1.5.5 Identifying common and drug-related adverse events

Overall, 77 (25%) unblinded subjects in LAM100034 and LAM100036 experienced AEs that were judged to be reasonably attributable to study drug by the investigator (Table 46). Dizziness (10 %) was the most frequently reported drug-related TEAE. In descending order, the next most frequent TEAEs considered to be reasonably caused the XR LTG were headache, nausea, somnolence, diplopia, asthenia, tremor, vomiting, vertigo, rash, blurred vision, abnormal coordination, and balance disorder.

Table 46 TEAEs Considered Reasonably Attributable to Study Drug Occurring in More than One Subject (Safety Population: Studies LAM100034 and LAM100036- Combined)

Adverse Event	Number (%) of Subjects		
	LAM100034 Double-Blind Treatment Phase		LAM100034 and LAM100036 Combined
	Placebo N=121	LTG XR N=118	LTG XR N=311
Any Event	23 (19)	42 (36)	77 (25)
Dizziness	2 (2)	17 (14)	32 (10)
Headache	4 (3)	8 (7)	14 (5)
Nausea	2 (2)	4 (3)	13 (4)
Somnolence	3 (2)	6 (5)	10 (3)
Diplopia	0	4 (3)	8 (3)
Asthenia	0	5 (4)	6 (2)
Tremor	1 (<1)	3 (3)	6 (2)
Vomiting	0	2 (2)	6 (2)
Vertigo	0	3 (3)	6 (2)
All Rash[a,b]	0	1 (<1)	6 (2)
Vision blurred	2 (2)	4 (3)	5 (2)
Coordination abnormal	0	3 (3)	5 (2)
Balance disorder	0	1 (<1)	4 (1)
Anxiety	0	2 (2)	4 (1)
Fatigue	1 (<1)	1 (<1)	4 (1)
Nystagmus	0	3 (3)	3 (<1)
Dry mouth	2 (2)	2 (2)	3 (<1)
Diarrhoea	1 (<1)	2 (2)	3 (<1)
Constipation	0	2 (2)	3 (<1)
Insomnia	3 (2)	1 (<1)	3 (<1)
Flatulence	0	1 (<1)	3 (<1)
Weight increased	1 (<1)	1 <1)	3 (<1)
Back pain	0	2 (2)	2 (<1)
Pruritus	3 (2)	0	0

Data Source: Table 5.34; LAM100034 CSR, Table 8.15
a. In LAM100034, terms comprising 'All Rash' category in LAM100034 included: rash generalised.
b. In LAM100034 and LAM100036 combined, terms comprising 'All Rash' category in LAM100034 included: rash, rash generalised, rash papular.

Reviewer Comment

- In general, the frequency of the TEAEs reasonably attributed to XR LTG was similar for the placebo-controlled phase and for the integrated analyses of patients in studies LAM100034 and LAM100036.

The vast majority of these TEAEs considered reasonably attributed to study drug were also identified in

- Table 41 as TEAEs occurring at any time in the study with a treatment effect (XR lamotrigine % - Placebo %) $\geq$ 2.0 %, suggesting that the XR caused this TEAE. Most of the TEAEs not appearing in
-
-
- Table 41 occurred as the least frequent TEAEs in Table 46 describing TEAEs thought to be related to XR treatment.

7.1.5.6 Additional analyses and explorations

- See section 7.1.4

7.1.6 Less Common Adverse Events

- See incidence of "low" frequency TEAEs in
-
-
- Table 41 and Table 43.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The sponsor collected data on many clinical laboratory analytes (e.g. hematology, clinical chemistry, urinalyses) in the only randomized, double-blind, placebo-controlled study (LAM100034) supporting this NDA. **However, several clinical chemistry analytes (e.g. serum calcium, phosphorus, LDH, cholesterol, triglycerides, uric acid, chloride, bicarbonate, CPK) that are typically considered as standard for collection to provide a comprehensive clinical laboratory picture of safety were not collected and measured.**

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

I focused on analyzing and presenting the data from the only randomized, double-blind, placebo-controlled study (LAM100034) that was submitted in the sNDA.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology Data

The sponsor presented the mean absolute hematology analyte data and change from baseline over time (visits 4, 6, 8, and end of study visit for end of study or early study discontinuation).

Reviewer Comment

- There were no remarkable changes throughout the study for either mean absolute data or change from baseline over time.

Chemistry Data

The sponsor presented the mean absolute chemistry analyte data and change from baseline over time (visits 4, 6, 8, and end of study visit for end of study or early study discontinuation).

Reviewer Comment

- There were no remarkable changes throughout the study for either mean absolute data or change from baseline over time.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Hematology Data

The sponsor noted that there were no remarkable changes from baseline (e.g. to high or low values relative to the reference range) for lamotrigine XR (vs placebo) for treatment over time or throughout the whole study (

Table 47).

Table 47 Hematology Changes from Baseline to Low or to High Relative to the Reference Range Throughout the Study (Safety Population: Study LAM100034)

Parameter/Change Category	Reference Range	PBO N=121 n/N (%)	LTG XR N=118 n/N (%)
Eosinophils (%)	To High	9/103 (9)	6/107 (6)
Eosinophils (GI/L)	To Low	7/101 (7)	6/107 (6)
	To High	4/101 (4)	5/107 (5)
Hematocrit (%)	To Low	9/102 (9)	5/108 (5)
	To High	0	4/108 (4)
Hemoglobin (G/L)	To Low	10/102 (10)	8/108 (7)
	To High	0	1/108 (<1)
Lymphocytes (%)	To Low	4/103 (4)	3/107 (3)
	To High	3/103 (3)	4/107 (4)
Lymphocytes (GI/L)	To Low	3/101 (3)	1/107 (<1)
	To High	1/101 (<1)	0
Mean Corpuscle Hemoglobin (PG)	To Low	0	3/108 (3)
	To High	5/102 (5)	3/108 (3)
Mean Corpuscle Hemoglobin Concentrate (G/L)	To Low	2/102 (2)	3/108 (3)
Mean Corpuscle Volume (FL)	To Low	0	4/108 (4)
	To High	3/102 (3)	4/108 (4)
Monocytes (%)	To High	4/103 (4)	2/107 (2)
Monocytes (GI/L)	To Low	3/101 (3)	7/107 (7)
Platelet Count (GI/L)	To Low	0	1/107 (<1)
	To High	1/101 (<1)	2/107 (2)
Red Blood Cell Count (TI/L)	To Low	9/102 (9)	7/108 (6)
Segmented Neutrophils (%)	To Low	3/103 (3)	2/107 (2)
	To High	3/103 (3)	3/107 (3)
Segmented Neutrophils (GI/L)	To Low	3/101 (3)	4/107 (4)
	To High	1/101 (<1)	1/107 (<1)
Total Neutrophils (%)	To Low	3/89 (3)	1/93 (1)
	To High	3/89 (3)	3/93 (3)
Total Neutrophils (GI/L)	To Low	1/87 (1)	4/93 (4)
	To High	1/87 (1)	1/93 (1)
White Blood Cell Count (GI/L)	To Low	1/101 (<1)	4/107 (4)
	To High	2/101 (2)	2/107 (2)

Data Source: Table 8.24

Reviewer Comment

- The treatment difference frequency for the shift to low (below reference range) showed a notable difference for XR lamotrigine treatment for total WBC (≥ 3 %), total neutrophils (3 %), and total monocytes (4 %). Although there did not appear to be any serious blood dyscrasias in this study, the IR lamotrigine label includes a warning for various "low" blood dyscrasias including leukopenia, neutropenia, and other abnormalities.

Consequently, it does not seem surprising if XR caused these low white cell abnormalities. It may be appropriate to note the distinct development of low monocytes in the label as this specific abnormality does not appear in the IR lamotrigine label.

Chemistry Data

There were no remarkable changes from baseline (e.g. to high or low values relative to the reference range) for lamotrigine XR (vs placebo) for treatment over time or throughout the whole study (Table 48).

Table 48 Chemistry Changes from Baseline to Low or to High Relative to the Reference Range (Safety Population: Study LAM100034)

Parameter/Change Category	Reference Range	PBO N=121 n/N (%)	LTG XR N=118 n/N (%)
Alanine Amino Transferase (IU/L)	To High	3/114 (3)	1/111 (<1)
Albumin (G/L)	To Low	1/114 (<1)	0
	To High	3/114 (3)	6/111 (5)
Alkaline Phosphatase (IU/L)	To Low	1/114 (<1)	0
	To High	2/114 (2)	2/111 (2)
Aspartate Amino Transferase (IU/L)	To High	0	1/110 (<1)
Creatine (UMOL/L)	To High	2/114 (2)	0
Glucose	To Low	7/114 (6)	3/111 (3)
	To High	8/114 (7)	10/111 (9)
Potassium (MMOL/L)	To Low	2/114 (2)	0
	To High	2/114 (2)	2/110 (2)
Sodium (MMOL/L)	To Low	2/114 (2)	3/111 (3)
Total Bilirubin (UMOL/L)	To High	0	1/111 (<1)
Total Protein (G/L)	To Low	1/114 (<1)	0
Urea (MMOL/L)	To Low	3/114 (3)	3/111 (3)
	To High	3/114 (3)	0

Data Source: Table 8.28

Reviewer Comment

- The treatment difference frequency for the shift to high glucose was slight (2 %).

Urinalysis Data

There were no clear remarkable/noteworthy effects of lamotrigine XR treatment on urinalyses throughout the study

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Abnormalities of Potential Clinical Concern

Hematology Data

There were no apparent trends in the proportions of subjects with hematology values outside of the laboratory reference range that were considered as markedly abnormal values that were abnormalities of clinical concern.

Chemistry Data
There were no apparent trends in the proportions of subjects with hematology values outside of the laboratory reference range that were considered as markedly abnormal values that were abnormalities of clinical concern.
Urinalysis Data
There were no clear remarkable/noteworthy effects of lamotrigine XR treatment on urinalyses throughout the study.

Reviewer Comment

- I reviewed the sponsor's threshold criteria for values that were PCC along with the reference range and the sponsor's criteria appeared to be reasonable.

- I agree with the sponsor that there were no clear suggestions of clinical laboratory changes of PCC for XR lamotrigine treatment based upon the XR treatment effect and considering the % of PCC values at screening in each treatment group.

7.1.7.4 Additional analyses and explorations

- Not applicable

7.1.7.5 Special assessments

- Not applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The sponsor did not make any special efforts to collect nor analyze vital signs (VS). The LAM100034 protocol noted that vital signs (systolic and diastolic blood pressure, pulse) were to be collected at each study visit. However, there was no specification to measure orthostatic VS, to collect VS in any specific position nor after following any specific procedure, nor to measure VS at any particular relationship to dosing of study treatment.
The sponsor did not plan to collect any VS in the open-label continuation/extension phase.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The sponsor collected VS measurements in all clinical studies. However, my focus in this review is to present data analyses primarily from the placebo-controlled phase of study LAM100034

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The sponsor provided a summary of absolute mean vital signs (blood pressure and pulse) over time and the change from baseline in vital signs. The sponsor noted that there were no changes of clinical importance in mean changes from Baseline and suggested that there was no evidence from values reported from vital signs that suggest any systematic drug effect.

Reviewer Comment

- The mean change from baseline for SBP over time (all visits from 3-8) showed a mild, mean decreased treatment effect (mean XR lamotrigine – mean Placebo) at all visits ranging from – 1.1 to -2.7 mm Hg. The mean treatment effect decrement at the final study visit (week 19) was – 2.3 for "completers" and the mean treatment effect decrement at the final study visit (week 19 or last visit when premature study discontinuation) was -2.6.

- The mean change from baseline for DBP over time (all visits from 3-8) showed a mild, mean decreased treatment effect (mean XR lamotrigine – mean Placebo) at all visits ranging from – 0.5 to – 1.8 mm Hg. The mean treatment effect decrement at the final study visit (week 19) was – 0.5 for "completers" and the mean treatment effect decrement at the final study visit (week 19 or last visit when premature study discontinuation) was -1.2.

- The mean change from baseline for pulse over time (all visits from 3-8) showed a mild, mean decreased treatment effect (mean XR lamotrigine – mean Placebo) at all visits ranging from – 0.7 to – 1.6 mm Hg. The mean treatment effect decrement at the final study visit (week 19) was – 1.1 for "completers" and the mean treatment effect decrement at the final study visit (week 19 or last visit when premature study discontinuation) was -1.6.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

A summary of vital signs outside the reference range and changes (to "high" or "low" values) from baseline relative to the reference range was provided.. The majority of subjects had no change from Baseline in vital signs. No subjects had changes to low. Table 49 summarizes the subjects with vital sign changes from Baseline to high relative to the reference range. **No patients were reported to have changes from baseline to "low" values relative to the reference range in either treatment group for any of the VS parameters.**

Table 49 Frequency of Vital Sign Changes from Baseline to High Relative to the Reference Range (Safety Population: Study LAM100034)

Parameter/Change Category	Reference Range	PBO N=121 n (%)	LTG XR N=118 n (%)
Systolic Blood Pressure	To High	11 (9)	7 (6)
Diastolic Blood Pressure	To High	3 (2)	8 (7)
Heart Rate	To High	0	1 (1)

Data Source: Table 8.34

The frequency of Change from Baseline to Low was noted to be 0 for all VS parameters for all visits. In contrast , the frequency of Change from Baseline to High was detectable for all VS parameters (and usually quite notable, often ≥ 7 % for SBP and DBP for all visits) usually for both treatment groups.

Reviewer Comment

- **The sponsor's overall approach for analyzing VS outliers was not only not very sophisticated or sensitive, but in particular it was either inappropriate or absent for identifying "low" VS outliers.** An outlier occurred when a VS parameter was considered high or low relative to the reference range. Of interest, at each visit in the placebo-controlled phase, there were various % of patients who exhibited a high VS (for systolic and diastolic blood pressure, and pulse), but were there never any patients who were outlier for "low" VS for any parameter at any visit. The value "0" was noted in every instance. Of additional interest, there was no description of what was the reference range for each VS parameter. When I referred to a listing (Table 9.35) including patients who exhibited outlier values for VS, the following reference "normal range" was identified for SBP (NA-139), for DBP (NA-89) and pulse (35 -100). There was no specification as to whether NA meant "not available" or "not applicable."

  After reviewing the listing information in Table 9.35 of the final study report, it was readily apparent why there were no "low" outliers for any VS parameter at any visit! It is impossible to identify an outlier below a certain "low" threshold value when there is no such threshold value. Thus, it was not possible to identify any "low" outliers for SBP or DBP. Given this strange, inexplicable approach, I consider it clearly inappropriate and misleading to have noted that there were 0 "low" VS outliers in the summary analysis tables. Furthermore, specifying that the lower "normal" reference limit for pulse is 35 is also clearly inappropriate on a clinical basis. A pulse of 35 could be compatible with a heart rate associated with complete heart block! Extremely rare, healthy subjects (e.g. perhaps some world class aerobic athletes) could have a "normal" resting heart rate as slow as 35! A typical "normal" range for heart rate is usually 60-100.
  To address the sponsor's shortcomings in analyzing VS outliers, I requested that the sponsor conduct and submit additional VS outlier analyses (see section 7.1.8.4).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Reviewer Comment

- The sponsor did not analyze and present patient VS data for marked outliers nor for dropouts for VS outlier abnormalities

7.1.8.4 Additional analyses and explorations

I requested that the sponsor conduct additional outliers for moderate and markedly abnormal outliers for VS. The following outlier thresholds for each positional analysis (supine, standing, change from supine to standing) were requested : 1) $\geq$ 20 mm Hg SBP increment or decrement; 2) $\geq$ 40 mm Hg SBP increment or decrement; 3) $\geq$ 10 mm Hg DBP increment or decrement; 4) $\geq$ 20 mm Hg DBP increment or decrement; 5) $\geq$ 15 beats per minute increment or decrement; and 6) $\geq$ 30 beats per minute increment or decrement.

Table 50 Incidence of Change from Baseline VS (SBP, DBP, Pulse) Outliers for Lamotrigine XR Treatment (vs Placebo) and Treatment Effect (LTG XR-Placebo) Over Time in Study Controlled Phase of Study LAM100034

Vital Sign	Treatment	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
SBP Inc>=20	LTG	2/111 (2%)	5/105 (5%)	1/ 98 (1%)	3/ 97 (3%)	5/108 (5%)
SBP Inc>=20	Placebo	7/119 (6%)	6/117 (5%)	6/112 (5%)	3/108 (3%)	3/113 (3%)
SBP Inc>=20	Rx Effect	-4%	-0%	-4%	0%	2%
SBP Inc>=40	LTG	0/111 (0%)	0/105 (0%)	1/ 98 (1%)	0/ 97 (0%)	0/108 (0%)
SBP Inc>=40	Placebo	1/119 (<1%)	0/117 (0%)	1/112 (<1%)	1/108 (<1%)	0/113 (0%)
SBP Inc>=40	Rx Effect	-1%	0%	0%	-1%	0%
DBP Inc>=10	LTG	14/111 (13%)	16/105 (15%)	11/ 98 (11%)	7/ 97 (7%)	14/108 (13%)
DBP Inc>=10	Placebo	15/119 (13%)	7/117 (6%)	14/112 (13%)	15/108 (14%)	6/113 (5%)
DBP Inc>=10	Rx Effect	0%	9%	-1%	-7%	8%
DBP Inc>=20	LTG	2/111 (2%)	2/105 (2%)	1/ 98 (1%)	1/ 97 (1%)	1/108 (<1%)
DBP Inc>=20	Placebo	1/119 (<1%)	2/117 (2%)	0/112 (0%)	2/108 (2%)	1/113 (<1%)
DBP Inc>=20	Rx Effect	1%	0%	1%	-1%	0%
SBP Dec<=20	LTG	4/111 (4%)	3/105 (3%)	6/ 98 (6%)	11/ 97 (11%)	5/108 (5%)
SBP Dec<=20	Placebo	4/119 (3%)	9/117 (8%)	7/112 (6%)	10/108 (9%)	6/113 (5%)
SBP Dec<=20	Rx Effect	0%	-5%	-0%	2%	-1%
SBP Dec<=40	LTG	0/111 (0%)	0/105 (0%)	0/ 98 (0%)	1/ 97 (1%)	0/108 (0%)
SBP Dec<=40	Placebo	0/119 (0%)	2/117 (2%)	1/112 (<1%)	1/108 (<1%)	1/113 (<1%)
SBP Dec<=40	Rx Effect	0%	-2%	-1%	0%	-1%

DBP Dec<=10	LTG	16/111 (14%)	11/105 (10%)	13/ 98 (13%)	19/ 97 (20%)	19/108 (18%)
DBP Dec<=10	Placebo	11/119 (9%)	20/117 (17%)	17/112 (15%)	21/108 (19%)	18/113 (16%)
DBP Dec<=10	Rx Effect	5%	-7%	-2%	0%	2%
DBP Dec<=20	LTG	1/111 (<1%)	0/105 (0%)	0/ 98 (0%)	2/ 97 (2%)	1/108 (<1%)
DBP Dec<=20	Placebo	0/119 (0%)	4/117 (3%)	4/112 (4%)	3/108 (3%)	3/113 (3%)
DBP Dec<=20	Rx Effect	1%	-3%	-4%	-1%	-2%
Pulse Inc>=15	LTG	5/112 (4%)	8/106 (8%)	9/ 99 (9%)	5/ 98 (5%)	8/109 (7%)
Pulse Inc>=15	Placebo	2/119 (2%)	11/117 (9%)	7/112 (6%)	9/108 (8%)	4/113 (4%)
Pulse Inc>=15	Rx Effect	3%	-2%	3%	-3%	4%
Pulse Inc>=30	LTG	0/112 (0%)	0/106 (0%)	3/ 99 (3%)	2/ 98 (2%)	0/109 (0%)
Pulse Inc>=30	Placebo	0/119 (0%)	1/117 (<1%)	2/112 (2%)	1/108 (<1%)	0/113 (0%)
Pulse Inc>=30	Rx Effect	0%	-1%	1%	1%	0%
Pulse Dec<=15	LTG	3/112 (3%)	3/106 (3%)	5/ 99 (5%)	3/ 98 (3%)	4/109 (4%)
Pulse Dec<=15	Placebo	3/119 (3%)	4/117 (3%)	5/112 (4%)	2/108 (2%)	4/113 (4%)
Pulse Dec<=15	Rx Effect	0%	-1%	1%	1%	0%
Pulse Dec<=30	LTG	0/112 (0%)	0/106 (0%)	0/ 99 (0%)	0/ 98 (0%)	0/109 (0%)
Pulse Dec<=30	Placebo	0/119 (0%)	0/117 (0%)	0/112 (0%)	0/108 (0%)	0/113 (0%)
Pulse Dec<=30	Rx Effect	0%	0%	0%	0%	0%

LTG = Lamotrigine; Rx Effect (LTG% - Placebo%)
Systolic Blood Pressure and Diastolic Blood Pressure were measured in mmHg; Pulse was measured in BPM.
Baseline for each patient was the average of all vital sign measurements in the screen and baseline phase.

Table 51 Incidence of Change from Baseline VS (SBP, DBP, Pulse) Outliers for Lamotrigine XR Treatment (vs Placebo) and Treatment Effect (LTG XR-Placebo) in Titration and/or Maintenance Phases of Controlled Phase of Study LAM100034

Vital Sign	Treatment	Titration	Maintenance	Persisting	Whole Study
SBP Inc>=20	LTG	4/113 (4%)	8/105 (8%)	1/105 (<1%)	11/113 (10%)
SBP Inc>=20	Placebo	9/120 (8%)	12/115 (10%)	3/115 (3%)	15/120 (13%)
SBP Inc>=20	Rx Effect	-4%	-3%	-2%	-3%
SBP Inc>=40	LTG	0/113 (0%)	1/105 (<1%)	0/105 (0%)	1/113 (<1%)
SBP Inc>=40	Placebo	1/120 (<1%)	2/115 (2%)	0/115 (0%)	3/120 (3%)
SBP Inc>=40	Rx Effect	-1%	-1%	0%	-2%
DBP Inc>=10	LTG	23/113 (20%)	21/105 (20%)	4/105 (4%)	37/113 (33%)
DBP Inc>=10	Placebo	15/120 (13%)	27/115 (23%)	2/115 (2%)	36/120 (30%)
DBP Inc>=10	Rx Effect	8%	-3%	2%	3%
DBP Inc>=20	LTG	2/113 (2%)	3/105 (3%)	1/105 (<1%)	4/113 (4%)
DBP Inc>=20	Placebo	1/120 (<1%)	5/115 (4%)	0/115 (0%)	6/120 (5%)
DBP Inc>=20	Rx Effect	1%	-1%	1%	-1%
SBP Dec<=20	LTG	6/113 (5%)	14/105 (13%)	1/105 (<1%)	17/113 (15%)
SBP Dec<=20	Placebo	8/120 (7%)	15/115 (13%)	2/115 (2%)	18/120 (15%)
SBP Dec<=20	Rx Effect	-1%	0%	-1%	0%
SBP Dec<=40	LTG	0/113 (0%)	1/105 (<1%)	0/105 (0%)	1/113 (<1%)
SBP Dec<=40	Placebo	1/120 (<1%)	1/115 (<1%)	0/115 (0%)	2/120 (2%)
SBP Dec<=40	Rx Effect	-1%	0%	0%	-1%

DBP Dec<=10	LTG	21/113 (19%)	31/105 (30%)	4/105 (4%)	40/113 (35%)
DBP Dec<=10	Placebo	16/120 (13%)	38/115 (33%)	7/115 (6%)	45/120 (38%)
DBP Dec<=10	Rx Effect	5%	-4%	-2%	-2%
DBP Dec<=20	LTG	1/113 (<1%)	2/105 (2%)	0/105 (0%)	3/113 (3%)
DBP Dec<=20	Placebo	1/120 (<1%)	7/115 (6%)	0/115 (0%)	8/120 (7%)
DBP Dec<=20	Rx Effect	0%	-4%	0%	-4%
Pulse Inc>=15	LTG	8/114 (7%)	18/106 (17%)	2/106 (2%)	22/114 (19%)
Pulse Inc>=15	Placebo	7/120 (6%)	16/115 (14%)	1/115 (<1%)	22/120 (18%)
Pulse Inc>=15	Rx Effect	1%	3%	1%	1%
Pulse Inc>=30	LTG	0/114 (0%)	5/106 (5%)	0/106 (0%)	5/114 (4%)
Pulse Inc>=30	Placebo	0/120 (0%)	4/115 (3%)	0/115 (0%)	4/120 (3%)
Pulse Inc>=30	Rx Effect	0%	1%	0%	1%
Pulse Dec<=15	LTG	5/114 (4%)	8/106 (8%)	2/106 (2%)	9/114 (8%)
Pulse Dec<=15	Placebo	6/120 (5%)	7/115 (6%)	1/115 (<1%)	11/120 (9%)
Pulse Dec<=15	Rx Effect	-1%	1%	1%	-1%
Pulse Dec<=30	LTG	0/114 (0%)	0/106 (0%)	0/106 (0%)	0/114 (0%)
Pulse Dec<=30	Placebo	0/120 (0%)	0/115 (0%)	0/115 (0%)	0/120 (0%)
Pulse Dec<=30	Rx Effect	0%	0%	0%	0%

LTG = Lamotrigine; Rx Effect (LTG% - Placebo%)
Systolic Blood Pressure and Diastolic Blood Pressure were measured in mmHg; Pulse was measured in BPM.
Baseline for each patient was the average of all vital sign measurements in the screen and baseline phase.
Titration = occurring during titration period. Maintenance = occurring during maintenance period.
Persisting = occurring during titration period and persisting into maintenance period.
Whole study = occurring at any time during titration and/or maintenance period.
Outlier vital signs assessed after the end of double blind treatment are not included in the Titration, Maintenance, or the Whole Study columns. However, these visits are included in the by-visit columns on the recorded treatment visit number.

Reviewer Comment

- My requested analyses of VS outliers over time showed several timepoints for different parameters and threshold outliers when the treatment effect (XR lamotrigine % - Placebo %) was positive (i.e. ≥ 1 %) (Table 50). I will point out positive treatment effects when ≥ 2 %.

  There was an increased (≥ 2 %) treatment effect for mild-moderate SBP and DBP increments at the final scheduled visit (week 19). The DBP treatment effect was quite notable at 8 % at the end of the study and was also notable (9 %) at the end of the titration period (week 7).

  There was an increased (≥ 2 %) treatment effect for mild-moderate SBP and DBP decrements, at week 15 for SBP, and at week 3 and at the final visit for DBP.

  The only notable outlier change for pulse was for a mild-moderate increment at weeks 3, 11, and 19.

- Table 51 shows the outlier analyses for these same parameter and thresholds from a somewhat different perspective. This perspective is based upon the incidence at any time in the titration period (weeks 3 and/or 7), in maintenance period (weeks 11, 15, and 19), in either titration and/or maintenance period, and when "persisting" (for ≥ 7 days) from the titration period into the maintenance period.

  In these analyses, there was an increased (≥ 2 %) treatment effect for mild-moderate DBP increment in the titration period (especially notable - 9 %), in the whole study period, and for "persisting."

There was also an increased (≥ 2 %) treatment effect for mild-moderate DBP decrement in the titration period.

The only notable outlier change for pulse was for a mild-moderate increment in the maintenance period. Of potential relevance to this observation, the sponsor noted that a consistent, small increase in heart rate was observed on IR lamotrigine compared with placebo in the sponsor's "thorough" QTc study SCA104648.

- Some notable VS changes may warrant inclusion/description in the label.

- **It is also important to note that the sponsor's analysis plan for vital sign changes only included the selected data such as only the last set of VS collected at visit 3 (immediately prior to randomization and initiation of treatment) as the "baseline" VS for subsequent comparison of all post-treatment effects.** This approach was taken despite the fact that a total of 3 sets of VS had been collected in the pre-treatment period at visit 1 (5-10 weeks prior to treatment initiation), and visit 2 (4 weeks prior to treatment initiation). Unfortunately, the sponsor did not combine and average all pre-treatment sets of VS to obtain an integrated average, that presumably could reflect an individual's typical VS values. Considering the concept of "regression to the mean," it is possible that the VS set collected immediately before treatment initiation may not have been representative of the typical VS values for that patient and therefore, a potential XR lamotrigine treatment effect may have been over- or underestimated.

- The above described analytical shortcoming was recognized too late in the review cycle to ask the sponsor to conduct repeat VS analyses using the mean of all pre-treatment VS as the "baseline" comparator for assessing all post-treatment changes of all VS analyses. If an approval letter is issued, I recommend that the sponsor repeat VS analyses and submit all VS analyses using the mean of all pre-treatment VS values as the "baseline."

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results.

The sponsor only planned to collect 2 ECGs in each patient, one during the screening phase (~ 8-10 weeks prior to initiating treatment in the DBP and at the end of the DBP at study visit 8 after 7 weeks in the titration phase and 12 weeks in the maintenance phase.

The sponsor also submitted a "thorough" QTc study (SCA104648) in which it evaluated increasing doses of IR lamotrigine for its effect on electocardiographic parameters including QTc. The DNP had noted at the pre-NDA meeting that results from this study would also apply to the risk for lamotrigine XR. This final study report (FSR) is being reviewed by the

CardoRenal QTc Team. Results from this study are presented separately in section 7.1.12 (Special Safety Studies).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

As with VS, my focus for ECG data (other than the "thorough" QTc study described in section 7.1.12 Special Safety Studies) is solely on the DBP of study LAM100034.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

The mean absolute data for each ECG parameter (i.e. heart rate, QTcBazett-QTcB, PR, QRS) were relatively similar at the screening visit and the last scheduled visit of the DBP (visit 8) and not clearly remarkable. The change from screening for heart rate and QRS duration for placebo and XR treatment were also minimal and similar and not remarkable (Table 53). The change from screening for treatment effect (XR Lamotrigine – Placebo) for the P-R interval was 8.4 msecs and the 95 % confidence interval overlapped with positive and negative numbers. With regard to these results The sponsor noted that the change from Screening to Endpoint in heart rate, PR interval, QTc Bazett, and QRS duration were not significantly different between the two treatment groups.

The sponsor conducted additional analyses for QTc during the review (in response to my request) and provided results for QTc Fridericia correction (QTcF) data because these had not been provided and the original change from screening to the end of study for QTcB had indicated a XR lamotrigine treatment effect of ~ 7 msecs. In addition, the sponsor subsequently conducted repeat QTc analyses because it recognized (after I raised a question) that it had conducted QTc analyses using an erroneous and markedly low raw QT of 12.9 msecs at screening in a lamotrigine treated patient (# 2146). I am presenting the results of the corrected QTc analyses and also summary QTc outlier results for change from screening for $\geq$ 30 msecs and $\geq$ 60 msecs that had not been presented.

The repeat QTc analyses for change from screening are shown in Table 53. These results show a change from screening treatment effect for QTcB of 4.4 msecs and for QTcF of 4.0 msecs. This minimally positive treatment effect for both QTcB and QTcF is due primarily to a decrease in the placebo group rather than an increment in the XR lamotrigine group. Although the safety results were not powered to show any specific changes, the 95 % confidence interval for both QTcB and QTcF include negative and positive numbers.

The sponsor also presented QTc change from screening analyses according to modal XR lamotrigine dose (Table 54) in response to my request.

Table 52 Change from Screening to End of Study for ECG Parameters (RR, PR, QRS)

		PBO (N=121)	Lamictal XR (N=118)	95% CI
Heart Rate (bpm)	N	109	107	(-3.1,2.3)
	Mean	0.5	0.9	
	SD	10.61	9.43	
	Median	0.0	1.0	
	Min	-19	-30	
	Max	27	24	
	95% CI#	(-1.5,2.5)	(-0.9,2.7)	
PR Interval (msec)	N	108	105	(-24.7,7.7)
	Mean	-4.5	3.9	
	SD	82.87	14.99	
	Median	0.0	0.0	
	Min	-593	-24	
	Max	140	100	
	95% CI#	(-20.4,11.3)	(1.0,6.8)	
QRS Duration (msec)	N	109	107	(-4.4,1.8)
	Mean	-0.5	0.8	
	SD	13.13	9.77	
	Median	0.0	0.0	
	Min	-69	-40	
	Max	46	38	
	95% CI#	(-3.0,2.0)	(-1.1,2.7)	

Table 53 Change from Screening to End of Study for QTc (Bazett, QTcB) and QTc (Fridericia, QTcF)

		PBO (N=121)	Lamictal XR (N=118)	95% CI
QTc - (Bazett) (msec)	N	108	103	(-11.1,2.3)
	Mean	-3.8	0.6	
	SD	26.51	22.63	
	Median	-4.5	0.0	
	Min	-74	-54	
	Max	96	60	
	95% CI#	(-8.9,1.2)	(-3.9,5.0)	
QTc - (Fridercia) (msec)	N	108	103	(-9.7,1.6)
	Mean	-4.5	-0.5	
	SD	22.61	19.12	
	Median	-3.7	0.0	
	Min	-73	-63	
	Max	93	55	
	95% CI#	(-8.8,-0.2)	(-4.2,3.3)	

Table 54 Change from Screening to End of Study for QTc (Bazett, QTcB) and QTc (Fridericia, QTcF) According to Modal Dose of XR Lamotrigine

		PBO (N=121)	LTG-XR <300 (N=36)	LTG-XR >=300-<500 (N=32)	LTG-XR >=500 (N=50)	95% CI - PBO vs: <300	95% CI - PBO vs: >=300-<500	95% CI - PBO vs: >=500
QTc - (Bazett) (msec)	N	108	29	28	46	(-18.7,2.7)		
	Mean	-3.8	4.2	-3.8	0.9		(-10.8,10.7)	
	SD	26.51	23.41	22.07	22.53			(-13.6,4.1)
	Median	-4.5	0.5	-0.5	-0.6			
	Min	-74	-36	-54	-54			
	Max	96	60	55	38			
	95% CI#	(-8.9,1.2)	(-4.7,13.1)	(-12.3,4.8)	(-5.8,7.6)			
QTc - (Fridercia) (msec)	N	108	29	28	46	(-17.4,0.7)		
	Mean	-4.5	3.8	-5.0	-0.4		(-8.8,9.7)	
	SD	22.61	18.60	19.31	19.10			(-11.6,3.4)
	Median	-3.7	0.6	-0.2	0.8			
	Min	-73	-30	-49	-63			
	Max	93	55	51	36			
	95% CI#	(-8.8,-0.2)	(-3.3,10.9)	(-12.5,2.5)	(-6.1,5.2)			

Reviewer Comment

- This minimally positive treatment difference does not raise serious questions. However, the study design of collecting a single ECG up to potentially 10 weeks before initiating treatment and collected a single ECG at the end of the study unrelated to lamotrigine doing is clearly an extremely insensitive study design for seriously detecting a QTc change related to XR lamotrigine treatment.

  I also note that the "thorough" QTc study that studied IR lamotrigine treatment up to 400 mg daily dosing in healthy subjects did not show any QTc prolongation.

- The analyses of QTc change from screening according to modal dose did not provide much additional insight. The greatest treatment effect for both QTcB and QTcF (~ 8 msecs for both was associated with the lowest modal daily dose (< 300 mg/d). The treatment effect for both QTcB and QTc was nearly 0 for the intermediate dose. The QTc treatment effect for QTcB and QTcF was ~ 4-5 msecs for the highest daily modal dose range (≥ 500 mg/d). Although positive treatment effect for QTc change from screening did not show a dose-response according to the modal daily dose, this is not too surprising considering that patients in the 3 different dose ranges would be expected to have similar plasma lamotrigine exposures. This is so because daily lamotrigine dose was highly correlated to the concomitant type/group of AED and a different XR target dose depending on the anticipated effect of the concomitant AED on plasma lamotrigine levels.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 55 Incidence of QTcB and QTcF Outliers for Change from Screening

Parameter	Treatment	Visit 8
QTc (Bazett) Inc>=30	LTG	8/103 (8%)
QTc (Bazett) Inc>=30	Placebo	5/108 (5%)
QTc (Bazett) Inc>=30	Rx Effect	3%
QTc (Bazett) Inc>=60	LTG	0/103 (0%)
QTc (Bazett) Inc>=60	Placebo	3/108 (3%)
QTc (Bazett) Inc>=60	Rx Effect	-3%
QTc (Fridercia) Inc>=30	LTG	5/103 (5%)
QTc (Fridercia) Inc>=30	Placebo	3/108 (3%)
QTc (Fridercia) Inc>=30	Rx Effect	2%
QTc (Fridercia) Inc>=60	LTG	0/103 (0%)
QTc (Fridercia) Inc>=60	Placebo	2/108 (2%)
QTc (Fridercia) Inc>=60	Rx Effect	-2%

Table 56 Incidence of QTcB and QTcF Outliers for Change from Screening According to Modal Daily Dose of XR Lamotrigine

Parameter	Treatment	Visit 8
QTc (Bazett) Inc>=30	LTG-XR <300	4/ 29 (14%)
	LTG-XR >=300-<500	1/ 28 (4%)
	LTG-XR >=500	3/ 46 (7%)
	Placebo	5/108 (5%)
	LTG-XR <300 Rx Effect	9%
	LTG-XR >=300-<500 Rx Effect	-1%
	LTG-XR >=500 Rx Effect	2%
QTc (Bazett) Inc>=60	LTG-XR <300	0/ 29 (0%)
	LTG-XR >=300-<500	0/ 28 (0%)
	LTG-XR >=500	0/ 46 (0%)
	Placebo	3/108 (3%)
	LTG-XR <300 Rx Effect	-3%
	LTG-XR >=300-<500 Rx Effect	-3%
	LTG-XR >=500 Rx Effect	-3%
QTc (Fridercia) Inc>=30	LTG-XR <300	3/ 29 (10%)
	LTG-XR >=300-<500	1/ 28 (4%)
	LTG-XR >=500	1/ 46 (2%)
	Placebo	3/108 (3%)
	LTG-XR <300 Rx Effect	8%
	LTG-XR >=300-<500 Rx Effect	1%
	LTG-XR >=500 Rx Effect	-1%
QTc (Fridercia) Inc>=60	LTG-XR <300	0/ 29 (0%)
	LTG-XR >=300-<500	0/ 28 (0%)
	LTG-XR >=500	0/ 46 (0%)
	Placebo	2/108 (2%)
	LTG-XR <300 Rx Effect	-2%
	LTG-XR >=300-<500 Rx Effect	-2%
	LTG-XR >=500 Rx Effect	-2%

Reviewer Comment

- The outlier analyses shown in Table 55 showed a slight treatment effect for QTcB (3 %) and for QTcF (2 %) for outliers with a $\geq$ 30 msec QTc increment from screening. There was no increased treatment effect for QTcB or QTcF for outliers a $\geq$ 60 msec QTc increment from screening.
- The QTc outlier analyses (Table 56) for the ranges of modal XR lamotrigine daily doses showed an increased treatment effect for QTc outliers for QTcB (9%) and for QTcF (8 %) for the lowest daily dose range (< 300 mg/d). There was no notable positive treatment effect for either QTcB or QTcF for both higher daily modal dose ranges (300-<500 mg/d, and $\geq$ 500 mg/d).

  The PK exposures for these 3 dose ranges correlate highly with VPA in most patients in the < 300 mg/d group, with "neutral" AEDs in most patients in the 300-< 500 mg/d group, and EIAEDs in most patients in the $\geq$ 500 mg/d group. In addition, PK exposure is considered to be relatively similar among all three dose ranges and all 3 concomitant AEDs groups. Thus, it seems difficult to make much of the one subgroup having an increment treatment effect for mild-moderate QTc increments and the other not having a positive treatment effect. Furthermore, there was no apparent signal for any QTc outliers with an increment $\geq$ 60 msecs.

In summary, it is difficult to have a serious concerns about QTc prolongation with XR lamotrigine from these study results. Although the "thorough" QTc study did not suggest QTc prolongation, this study of IR lamotrigine did not clearly study supratherapeutic levels of plasma lamotrigine. However, XR lamotrigine PK exposure is relatively, generally similar to that for IR lamotrigine with regard to Cmax and AUC (similar to slightly lower for XR vs IR).

The official consult (see section 7.1.12) of the "thorough" QTc Team, that is reviewing the sponsor's "thorough" QTc Study SCA104648 (for IR lamotrigine) was received at the end of the review cycle and did not identify QTc prolongation. However, the sponsor did not adequately explore suprathreshold doses (i.e. doses above the recommended dose range).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

- See sections 7.1.9.3.2 and 7.1.9.3.4.

7.1.9.4 Additional analyses and explorations

This reviewer requested that the sponsor conduct and submit additional analyses for QTcB and QTcF for change from screening and for respective outliers for any dose and also based upon various daily XR lamotrigine dose ranges. These analyses are shown in sections 7.1.9.2 and 7.1.9.3

7.1.10 Immunogenicity

- Not applicable

7.1.11 Human Carcinogenicity

- There was no information presented that was applicable to this topic.

7.1.12 Special Safety Studies

Study SCA104648 : "A study to evaluate the effect of repeat oral doses of lamotrigine on cardiac conduction as assessed by 12-Lead ECG as compared to placebo and single oral doses of moxifloxacin."

Study Synopsis
Brief Summary of Results : To characterize the profile of lamotrigine with reference to its effects on QT (in accordance with current regulatory guidelines/standards), this study assessed the effect of up to 200 mg twice-daily (bid) of lamotrigine Immediate Release at steady state on the QT interval in healthy volunteers; this dose was chosen based on tolerability. In addition, the study used moxifloxacin, a drug with known mild QTc prolongation, as a positive control, and

placebo. No prolongation of QTcF interval was observed in healthy volunteers at steady state 50 mg, 150 mg or 200 mg bid lamotrigine IR compared with placebo. Similar results were observed on QTcB interval. A consistent, small reduction in QTcF on lamotrigine compared with placebo was observed. A consistent, small increase in heart rate was observed on lamotrigine compared with placebo. No effect of lamotrigine on QRS duration or blood pressure was observed. The sensitivity of this study in assessing QT effects was confirmed since a clinically significant QT effect was observed using moxifloxacin 400 mg single-dose as a positive control. The geometric mean AUC and Cmax ratios indicated a dose proportional increase in the exposure to lamotrigine following multiple doses of 50, 150 and 200 mg bid. The statistical analysis of pre-dose concentrations confirmed that steady-state was achieved following 12 days dosing at 50, 150 and 200 mg lamotrigine bid. The PK/PD model indicated that there were statistically significant decreases and increases in individually corrected QT intervals over the concentration range studied for lamotrigine and moxifloxacin, respectively. Twelve subjects were withdrawn from the study due to AEs, four of whom were withdrawn due to drug-related AEs during the lamotrigine dosing period. There was one SAE of pulmonary tuberculosis in a subject taking placebo.

Initiation Date: 08 August 2005
Completion Date: 13 July 2006
Date of Report: 31 January 2007

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Investigator: Dr. Ulrike Lorch, MD, FRCA, MFPM.
Study centre: Richmond Pharmacology Ltd, Thornton Wing, Mayday Hospital, 530 London Road, Croydon, CR7 7YE, UK.

Objectives :
Primary
• To estimate the effect of steady state oral dosing of lamotrigine and single dose moxifloxacin on QTc interval on each active regimen relative to placebo.
Secondary
• To estimate the effect of steady state oral dosing of lamotrigine and single dose moxifloxacin on QTcB, RR and heart rate on each active regimen relative to placebo.
• To characterize the pharmacokinetics of steady state lamotrigine and single dose moxifloxacin and to investigate the concentration-QTc effect relationship for lamotrigine.

Endpoints:
Primary
• QTcF for each active regimen relative to placebo.
Secondary
For each active regimen relative to placebo:

• QTcB.
• QT and RR interval and heart rate.
• Area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (Cmax) and time to Cmax (Tmax), for plasma moxifloxacin and steady-state serum lamotrigine concentrations.

Study Design and Methodology : This was a five-session, sequential treatment, parallel-group study. Initially, subjects were randomized to one of two treatment groups, Treatment Group 1 or Treatment Group 2, according to a previously prepared randomization schedule. Approximately 150 subjects were planned for enrollment, with the aim of having a minimum of 50 evaluable subjects in each of the two treatment groups.

Subjects attended a screening assessment within 28 days prior to the start of Session 1.

During the single-blind treatment sessions (Session 1 and Session 2), subjects received an oral dose of either moxifloxacin 400 mg or placebo (subjects were randomly assigned to one of the four sequences). All subjects in both treatment groups 1 and 2 received either a single oral dose of 400 mg moxifloxacin or placebo on Day 1 in Session 1, then after a 7-day washout, subjects received the alternate treatment not administered in Session 1 (either moxifloxacin or placebo) on Day 1 of Session 2. On each session a full profile of electrocardiograms (ECGs) was recorded and pharmacokinetic samples were taken for 24 h post-dose. Sessions 1 and 2 were separated by a 7-day washout period.

The double-blind phase of the study (Sessions 3, 4 and 5) commenced after another 7-day washout period. Subjects randomly assigned to Treatment Group 1 received increasing doses of lamotrigine, while those assigned to Treatment Group 2 received placebo on each corresponding study day. An immediate release formulation of lamotrigine (the chewable dispersible tablet) was used in the study. The slow up-titration required to achieve steady state to minimize the occurrence of rash necessitated a long duration of dosing and this precluded a crossover design. Hence, although the moxifloxacin part was a 2-period cross-over, the comparison of lamotrigine versus placebo in the second part was across the two parallel groups.
To maintain the blind, subjects in each group received the same number of tablets. There was no washout period between Sessions 3, 4 and 5. On Day 42 (100 mg/day lamotrigine), Day 63 (300 mg/day lamotrigine) and Day 77 (400 mg/day lamotrigine), a full profile of ECGs was recorded and pharmacokinetic samples were taken for 12 h after the morning dose of study medication.

A full profile of ECGs and pharmacokinetic samples were obtained over 12 h post-dose on Day 42 (50 mg lamotrigine bid/placebo), Day 63 (150 mg lamotrigine bid/placebo) and Day 77 (200 mg lamotrigine bid/placebo).

ECGs were recorded in triplicate at each recording time point and manually measured by a central reader.
The total duration of the double-blind treatment phase was 87 days, with a follow-up visit within 7–14 days of the last dose of study medication.

Serial blood samples for pharmacokinetic analyses of plasma moxifloxacin and serum lamotrigine concentrations were collected at pre-dose and over a 24 h and 12 h period, respectively, following dosing. All blood samples were analyzed for lamotrigine and moxifloxacin using liquid chromatography-tandem mass spectroscopy (LC/MS/MS) and solid phase extraction methodologies.

Summary of Key criteria Inclusion Criteria : Healthy, non-smoking, male and female subjects aged 18–55 years inclusive. Female subjects were required to be either postmenopausal, have had a documented hysterectomy, or if of childbearing potential, to use an approved method of contraception. Subjects' body weight had to be ≥50 kg (110 lbs) and they had to have a body mass index within the range 18.5–29.9 kg/m^2 inclusive.

Summary of Key criteria Exclusion Criteria : Subjects were not eligible for inclusion in the study if they had a history of clinically significant disease, including: gastrointestinal, hepatic or renal disease, dermatological disease, drug-induced skin rash, fainting, family history of sudden death, orthostatic hypotension, seizure of any type, febrile convulsions, head injury, psychiatric illness, low blood pressure, ECG abnormality, and cardiovascular disease.

Treatment descriptions are shown in Table 57.

Table 57 Treatment Descriptions

Session	Treatment Group 1		Treatment Group 2[1]
Session 1	Day 1: Moxifloxacin 400 mg or moxifloxacin placebo (PK/ECG).		Day 1: Moxifloxacin or moxifloxacin placebo (PK/ECG).
Session 2	Day 1: Moxifloxacin 400 mg or moxifloxacin placebo (PK/ECG).		Day 1: Moxifloxacin or moxifloxacin placebo (PK/ECG).
Session 3	Lamotrigine:	Dose instructions:	
	Days 1-14: 25 mg.	1x25 mg am once-daily.	Days 1-42: lamotrigine placebo.
	Days 15-28: 50 mg.	1x25 mg am; 1x25 mg pm	
	Days 29-41:100 mg.	2x25 mg am; 2x25 mg pm	
	Day 42: 100 mg (PK/ECG).	2x25 mg am; 2x25 mg pm	Day 42: lamotrigine placebo (PK/ECG).
Session 4	Lamotrigine:		
	Day 43-49: 200 mg.	1x100 mg am; 1x100 mg pm	Days 43-62: lamotrigine placebo.
	Day 50-62: 300 mg.	1x100 mg + 2x25 mg am;	
	Day 63: 300 mg (PK/ECG).	1x100 mg + 2x25 mg pm 1x100 mg + 2x25 mg am; 1x100 mg + 2x25 mg pm	Day 63: lamotrigine placebo (PK/ECG).
Session 5	Lamotrigine:		
	Day 64-76: 400 mg	2x100 mg am; 2x100 mg pm	Days 64-76: lamotrigine placebo.
	Day 77: 400 mg (PK/ECG)	2x100 mg am; 2x100 mg pm	Day 77: lamotrigine placebo (PK/ECG).
Down-titration	Lamotrigine:		
	Day 78-79: 300 mg	1x100 mg + 2x25 mg am 1x100 mg + 2x25 mg pm	Days 78-85: lamotrigine placebo.
	Day 80-81: 200 mg	1x100 mg am; 1x100 mg pm	
	Day 82-83: 100 mg		
	Days 84-85: 50 mg	2x25 mg am; 2x25 mg pm 1x25 mg am; 1x25 mg pm	

1. To maintain blinding in Sessions 3, 4, 5 and down-titration subjects in Treatment Group 2 received the same number of tablets as subjects in Treatment Group 1.

PK = pharmacokinetics; ECG = electrocardiogram.

Subjects underwent a screening assessment within 28 days prior to the start of Session 1, a treatment phase of 87 dosing days and a follow-up visit within 7 to 14 days following the last dose of study medication.

Subjects who did not tolerate the 200 mg lamotrigine bid/placebo dose were to be down-titrated to a dose of 150 mg lamotrigine bid/placebo. The 150 mg lamotrigine bid/placebo dose would have been administered for at least 14 days, and subjects were to continue the study in accordance with the Session 5 study schedule. However, this procedure was not necessary for any subject in this study.

Criteria for evaluation: Pharmacodynamics: QTcF, QTcB, QT and RR interval and heart rate for each active regimen relative to placebo.

Pharmacokinetics: The pharmacokinetics of moxifloxacin following a single 400 mg oral dose were assessed by determining AUC(0–24), Cmax and tmax. The pharmacokinetics of lamotrigine following multiple oral doses of 50, 150 and 200 mg bid were assessed by determining AUC(0–12), Cmax and tmax.

Statistical methods :

Lamotrigine vs. placebo (Session 3 onwards): QTcF and QTcB (manual-read) were

analyzed separately by a repeated measures analysis of covariance, fitting regimen and time point and regimen*time point as fixed effect terms with covariate Session 3 pretreatment baseline and gender and pre-treatment baseline *time and subject as random.

The point estimates, and corresponding 90% confidence intervals, were calculated for the difference of Day 42 (for Lamotrigine 100 mg/day), Day 63 (for lamotrigine 300 mg/day) and Day 77 (for Lamotrigine 400 mg/day) compared with corresponding placebo at all time points using the appropriate error term.

Moxifloxacin vs. placebo (Session 1 and 2): QTcF and QTcB (manual-read) were analyzed separately by a repeated measures analysis of covariance, fitting sequence, regimen and time point and regimen*time point as fixed effect terms with covariate the corresponding session pre-treatment baseline and gender and pre-treatment baseline*time and subject as random. The point estimates for the differences between moxifloxacin and placebo, and corresponding 90% confidence intervals, for all time points were calculated using the appropriate error term.

Categorical analyses were performed to determine the number of subjects per regimen who had a maximum increase from baseline in manually read QTcF or QTcB ≤30 msec, >30 msec and >60 msec. Individual subjects who had a QTcF or QTcB value ≤450, >450, >480 and >500 msec were also summarized for each regimen.

Statistical analysis was performed to assess achievement of pharmacokinetic steady-state at days 42, 63 and 77 for doses 50, 150 and 200 mg bid lamotrigine, respectively.

Table 58 shows the disposition of subjects and Table 59 summarizes baseline demographic characteristics.

Table 58 Disposition of Subjects

Number of Subjects	Treatment Group 1	Treatment Group 2
Planned, N	75	75
Randomised, N	76	76
Completed, n (%)	50 (66)[1]	57 (75)
Total Withdrawn (any reason), n (%)	26 (34)	19 (25)
Withdrawn due to Serious Adverse Event, n (%)	0	1 (1)
Withdrawn due to Adverse Events, n (%)	9 (12)	3 (4)

1. In Table 9.6 (Summary of End of Study Record) Subject 800133 was recorded as being withdrawn on Day 77 of dosing due to severe adverse events. However, this Subject did not stop study medication but continued the down-titration period as scheduled and completed the study.

Table 59 Summary of Baseline Demographic Characteristics

		Treatment Group 1 N=76	Treatment Group 2 N=76
Sex, n (%)	Males	43 (57)	54 (71)
	Females	33 (43)	22 (29)
Age, years	Mean	27.1	26.9
	Range	18–50	18–50
Race, n (%)	White – White/Caucasian/European Heritage	55 (72)	58 (76)
	African American/African Heritage	14 (19)	8 (11)
	Asian – Central/South Asian Heritage	4 (5)	3 (4)
	Mixed Race	1 (1)	3 (4)
	White – Arabic/North African Heritage	0	2 (3)
	American Indian or Alaskan Native	1 (1)	1 (1)
	Asian – South East Asian Heritage	1 (1)	0
	Asian – East Asian Heritage	0	1 (1)

Pharmacodynamics No prolongation of QTcF was observed by 100 mg, 300 mg or 400 mg/day lamotrigine IR at steady state compared with placebo. Similar results were observed on QTcB interval. A small reduction in QTcF and a small increase in heart rate were observed at all lamotrigine doses studied.

The estimated difference in adjusted mean between 400 mg/day lamotrigine and placebo in QTcF over the 12-h period on Day 77 ranged from -7.48 msec to -2.81 msec, with 90% confidence intervals ranging from a low of -10.49 msec to a high of 0.20 msec, which excludes an effect ≥10 msec. The estimated difference in adjusted mean between 300 mg/day lamotrigine and placebo in QTcF over the 12-h period on Day 63 ranged from -6.76 msec to -1.50 msec, with 90% confidence intervals ranging from a low of - 9.66 msec to a high of 1.39 msec, which again excludes an effect ≥10 msec. The estimated difference in adjusted mean between 100 mg/day lamotrigine and placebo in QTcF over the 12-h period on Day 42 ranged from -4.41 msec to -0.73 msec, with 90% confidence intervals ranging from a low of -7.15 msec to a high of 2.29 msec. The sponsor noted that these confidence intervals exclude an effect ≥ 10 msec.

The estimated difference in adjusted mean QTcF between single-dose moxifloxacin 400 mg and single-dose placebo over the 24-h period on Day 1 from 0.5 h onward ranged from 6.00 to 14.81 msec. The greatest difference in QTcF for moxifloxacin compared with placebo was observed at 2.5 h post-dose. The 90% confidence interval at this time point demonstrates that the true mean difference could lie between 13.50 msec and 16.11 msec.

The sponsor said that the sensitivity of this study in assessing QT effects was confirmed since a clinically significant QT effect of prolongation was observed using moxifloxacin 400 mg single dose as a positive control in light of ICH-E14 Guidance.

Pharmacokinetics A summary of lamotrigine and moxifloxacin pharmacokinetic parameters is presented in Table 60.

Table 60 Summary of Pharmacokinetic Parameters By IR Lamotrigine Dose

Treatment	N	AUC(0–12)[1] (µg.h/mL)	Cmax[1] (µg/mL)	tmax[2] (h)
Lamotrigine 50 mg bid	54	25.7 (40.7)*****	2.59 (38.3)	1.12 (0, 4.12)
Lamotrigine 150 mg bid	52	69.6 (27.4)*	7.22 (24.7)***	1.08 (0.33, 3.08)***
Lamotrigine 200 mg bid	51	93.0 (23.5)**	9.61 (20.5)**	1.58 (0.33, 4.08)**
Moxifloxacin 400 mg[5]	142[4]	24100[3] (18.5)****	2280 (26.0)	1.60 (0.35, 6.10)

Source Data: Tables 12.1-12.4 and 12.9. * n = 50, ** n = 49, *** n = 51, **** n = 141, ***** n = 52.
1. Geometric mean (%CV).
2. Median (range).
3. AUC(0–24).
4. Subject 800149 was excluded as they vomited immediately after dosing and then withdrew from the study.
5. Concentration in ng/mL.
bid = twice-daily.

Safety : Analyses of TEAEs, reflecting safety, along with respective placebo controls at different time periods based upon randomized treatment over time did not suggest a different safety profile for IR lamotrigine than is already recognized.

One SAE (pulmonary tuberculosis) occurred in a subject taking placebo. Twelve subjects were withdrawn from the study due to AEs, of whom four were withdrawn due to drug related AEs during the lamotrigine dosing period. One of the 12 subjects was withdrawn because of increased aspartate transaminase and alanine transaminase values that resolved after withdrawal.

There were no unexpected clinical laboratory findings.

In the report, the sponsor noted the following findings. A summary of subjects with vital signs data outside the clinical concern range showed that very few values fell outside the clinical concern range with no apparent differences in the frequency of abnormal values on active treatments compared with placebo.

The sponsor also presented the mean changes from baseline before and after acute dosing on day 42, 63,and 77 in figures and in tables (along with 95% confidence intervals) for supine and standing SBP and DBP for each treatment.

In general, blood pressure was lower than baseline during treatment with both lamotrigine and placebo (i.e., the change from baseline was negative). At all time points the confidence intervals overlapped and were wide, particularly at the highest dose. In general, following dosing with lamotrigine 50 mg bid there were slightly smaller reductions in standing blood pressure values compared with placebo. However, the 95 % confidence intervals overlapped. There were similar supine blood pressure change from baseline values on lamotrigine 50 mg bid and placebo. Standing diastolic and systolic blood pressures had a slightly smaller reduction from baseline on placebo compared with lamotrigine 150 mg bid but all the confidence intervals overlapped. Systolic supine blood pressure had a slightly greater reduction on placebo than on 150 mg bid lamotrigine, however, again the confidence intervals all overlapped still. There was a smaller reduction in systolic blood pressure values on lamotrigine 200 mg bid compared with placebo, but the 95% confidence intervals did overlap.

Sponsor Conclusions:
• No prolongation of QTcF interval was observed in healthy volunteers at steady state 100 mg, 300 mg or 400 mg/day lamotrigine IR compared with placebo.
• Similar results were observed on QTcB interval.
• A consistent, small reduction in QTcF on lamotrigine compared with placebo was observed.
• A consistent, small increase in heart rate was observed on lamotrigine compared with placebo.
• No effect of lamotrigine on QRS duration or blood pressure was observed.
• The sensitivity of this study in assessing QT effects was confirmed since a clinically significant QT effect of prolongation was observed using moxifloxacin 400 mg single-dose as a positive control.
• The statistical analysis of pre-dose concentrations confirmed that steady-state was achieved following 12 days dosing at 50, 150 and 200 mg lamotrigine bid.
• The PK/PD model indicated that there was a statistically significant decrease in individually corrected QT intervals for lamotrigine and a statistically significant increase in individually corrected QT intervals for moxifloxacin over the concentration ranges studied.
• Twelve subjects were withdrawn from the study due to AEs, of whom four were withdrawn due to drug-related AEs during the lamotrigine dosing period. There was one SAE of pulmonary tuberculosis in a subject taking placebo. One of the 12 subjects was withdrawn because of increased aspartate transaminase and alanine transaminase values that resolved after withdrawal.

The following is the Summary (and some comments) of the Interdisciplinary Review Team for QT Studies Consultation for the sponsor's Thorough QT Study.

"SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Study SCA104648 was a 'thorough QT' study sponsored by GlaxoSmithKline and submitted to support NDA 22-115, an application to market an extended release formulation of a currently marketed product, LAMICTAL® (lamotrigine). The study attempted to assess the effect of administering immediate release lamotrigine on the QTc in healthy subjects. The study had multiple major deficiencies in design and conduct (see comments below). Nonetheless, the QT-IRT is persuaded by the sponsor's data that the highest plasma concentrations of lamotrigine likely to be achieved after administration of the highest recommended dose of immediate release or extended release LAMICTAL® will not prolong the QT interval. In fact, administration appears likely to shorten the QT interval modestly.

We do not accept the sponsor's assertion that study SCA104648 was a negative thorough QT study because the primary analysis was flawed for the reasons we review in our comments below. However, the results of the concentration-QT analysis show a trend to shorter QTc with increasing doses. In addition, an FDA conducted examination of the post-marketing database does not suggest that lamotrigine is associated with increased death rate, torsade de pointes or QT prolongation. Therefore the QT-IRT thinks it unlikely that lamotigine administration is associated with QT interval prolongation or serious ventricular arrhythmias. However, we

acknowledge that a different observer might reasonably come to a different conclusion given the flaws in study SCA104648.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

All of the following deficiencies tend to lower confidence in the reliability of the primary analysis.

• The exposures achieved in study SCA104648 failed to cover the highest exposures that can be reasonably expected to occur after administration of therapeutic doses of Lamictal and Lamictal XR. Co-administration of doses up to 250 mg with valproic acid are described in the PI. Taking PK interactions with valproic acid into account, this dose is equivalent to a monotherapy daily dose of 500 mg lamotrigine. The highest dose studied in this study was 200 mg bid. However other studies suggest that doses as high as 500 mg are not tolerable by healthy volunteers. Conducting a TQT study in patients with partial seizures might be challenging, as most of these patients would be on combination therapies confounding interpretation of the results.

• The sponsor conducted a two stage study with moxifloxacin administered to subjects only during the first stage. This design is problematic for the following reasons: 1) The effects on the QTc can be detected more sensitively since there were more subjects (and so more data) in the first stage; 2) The effects on the QTc can be detected more sensitively in the first stage because it was a crossover study so variance was reduced (since each subject served as their own control) compared with the parallel study conducted in the second stage; and 3) The period effect (stage 1 and stage 2) may be confounded by the treatment effect Therefore, using the first stage, which was conducted in a different way from the second stage, to claim assay sensitivity in the second stage is not valid.

Reviewer Comment

- I agree that there does not appear to be any QTc prolongation, but that there does appear to be some modest QTc shortening, a finding observed with some sodium channel inhibitors. However, I agree with the QT Interdisciplinary Review Team that the sponsor did not adequately study and explore suprathreshold doses of IR lamotrigine. The exposure of healthy subjects (who were not taking any concomitant AED) treated with IR lamotrigine 300 mg/day would be expected to be similar to the exposure in patients taking one or more "neutral" concomitant AEDs and 300 mg/day of IR lamotrigine. Thus, the administration of 400 mg/day of IR lamotrigine to healthy subjects would only result in an increased exposure of ~ 33 % above that expected in patients treated at the highest recommended dose for any of the concomitant AED groups.

- The sponsor conducted change from baseline analyses for each VS parameter (systolic blood pressure-SBP, diastolic blood pressure-DBP, and pulse) in supine and standing positions over time with the various treatments (placebo vs IR lamotrigine). Initially, the sponsor did not clearly identify whether one or more (or specifically which timepoint(s)

was used to determine the "baseline" and if so, whether the baseline represented a mean of several pre-treatment measurements. The sponsor also presented the changes from baseline before and after acute dosing on day 42, 63, and 77 in figures. I subsequently learned that the "baseline" was determined by a single dataset consisting of the last set of orthostatic VS collected prior to initiation of treatment with lamotrigine or placebo.

Thus, the sponsor followed a similar analytical approach for analyzing VS data as was used in study LAM100034. The sponsor used a single set of pre-treatment VS collected before treatment for comparison with all post-treatment results instead of averaging all pre-treatment VS collected (e.g. N = up to 7 pre-treatment "baseline" values at screening, at pre-dosing in session 1 and 2, at 2, 8, and 22-24 hours after placebo treatment in session 1 or 2, and at pre-dosing at day -1 prior to initiating lamotrigine or placebo in session 3) as each subject's "baseline" and then comparing this integrated/averaged baseline as the comparator for all post-treatment VS to determine treatment effects. Conceivably, different results could be demonstrated if a different, presumably more reliable/representative, "baseline" VS dataset was used for comparison to characterize effects of treatment instead of a single VS dataset that may not necessarily reflect the individual's "true baseline." It is highly desirable that all the orthostatic VS analyses be repeated using an integrated "baseline" orthostatic VS dataset (as post-treatment comparator) consisting of the average of all pre-treatment orthostatic VS.

- There were no clear mean change effects of lamotrigine with respect to acute dosing over time at steady state for 100, 300, or 400 mg lamotrigine (vs placebo).

- There did appear to be notable mean changes from baseline at the pre-dosing measurement on day 42 (50 mg BID), day 63 (150 mg BID), and day 77 (200 mg BID). The most striking mean changes from baseline noted at pre-dosing for 100 mg total dose (50 mg BID on day 42) were a slight ~ 1 mm decrease for standing DBP, and a moderate ~ 4 mm decrease for standing SBP. There were no remarkable changes for supine SBP and DBP.

  At the 300 mg total dose (150 mg BID on day 63), there was a mean ~ 3 mm decrease in supine SBP and a mean ~ 2 mm decrease in standing SBP at pre-dosing. There were no remarkable mean changes for supine or standing DBP.

  At the 300 mg total dose (150 mg BID on day 63), there was a mean ~ 2 mm decrease in supine SBP at pre-dosing. There were no remarkable mean changes for supine or standing DBP or standing SBP.

- Despite the fact that the sponsor did not note any outlier results suggesting an effect of lamotrigine, I believe that there were some outlier results that were potentially noteworthy based upon a notable treatment effect (i.e. lamotrigine % - placebo %). However, the way the sponsor presented the data it was difficult to assess what was occurring because there were so many variables (position, time after dosing, low or high incidence of clinical concern, treatment). In addition, these data were presented over

several pages making it difficult to interpret the data. Furthermore, the sponsor did not present its criteria for a low or high clinical concern outlier. The criteria were included in the Statistical Analysis Plan (SAP) that was not submitted until I requested it and the SAP did not clearly indicate how it applied outlier criteria of PCC. Of interest again, there were only outliers for high clinical concern outliers and none for low clinical concern outliers, raising the question that the same problems/deficiencies identified (in section 7.1.8) with outliers of potential clinical concerns for study 34.

Neither was there was a corresponding listing of individual subjects with these outliers of potential clinical concern (PCC). This information was requested and the sponsor then conducted analyses that were submitted on the day (9/20/07) before the action letter was to be issued. Despite, submitting new outlier analyses at this late time (9/20/07) in the review cycle because there was an "error" in the specific outlier criteria applied and that the sponsor applied these "new" criteria and repeated summary outlier analyses, the sponsor was still not able to confirm precisely what outlier criteria had been applied. For example, the sponsor could still not clarify whether change outlier criteria were also applied together with absolute threshold criteria for the original summary outlier analyses and the "new" summary outlier analyses and whether the new outlier listing provided on 9/20/07 was based solely upon outliers only for absolute threshold ranges. Obviously, these data were not able to be reviewed prior to issuing the action letter.

- **The sponsor's approach for analyzing outliers for various orthostatic VS parameters and presenting the results of these analyses was not a good one.** The sponsor had analyzed data and did not clearly indicate the criteria upon which the outliers had been analyzed and did not originally submit the critical, supplementary listing of subjects with outliers in the summary analyses. Furthermore, I thought that the PCC outlier criteria (SBP > 140 mm Hg; DBP > 90 mm HG) selected by the sponsor had the potential of not being of much clinical interest or concern or of being insensitive because it was not clear that a particular change (e.g. certain minimal increment was also required). Again it appeared that the sponsor did not have lower outlier threshold criteria for SBP and DBP, making it impossible to identify "low" outliers for these parameters!

- These data are of great potential interest for characterizing effects of lamotrigine on orthostatic vital signs but have not been analyzed and/or presented in a manner allowing one to make an adequate assessment of whether there were any notable effects. I believe that outlier analyses are potentially of great interest for characterizing individual responses that may be important to recognize and may be worthy of description in the label.

- I have also learned that the original data for orthostatic vital sign measurement submitted for the original lamotrigine NDA were also not appropriately analyzed or were analyzed in an insensitive manner. Combined outlier threshold criteria were applied and would not have identified as outliers of concern despite potential SBP increments or decrements that were $\geq$ 40 mm Hg (or more) and also large pulse changes may not have been identified. There was not outlier threshold for low DBP. The sponsor did not analyze the data for

dose response despite data for placebo, 300, and 500 mg lamotrigine daily. Results from studies collecting supine or sitting vital signs were combined and considered to represent "resting" values.

- In summary, requesting appropriate vital sign analyses (especially for outliers to characterize the risk for individual subjects) from placebo-controlled trials (especially also when orthostatic VS were measured) are highly desirable to characterize if there are potentially significant effects of lamotrigine on vital signs. If such changes are demonstrated, their description in the label may be warranted and potentially important. It is also of interest that dizziness is perhaps the most common TEAE with IR and XR lamotrigine but it is not clear if this TEAE is related to orthostatic hypotension/hypotension.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- There was no assessment of these topics.

7.1.14 Human Reproduction and Pregnancy Data

- There is no applicable information related to these topics

7.1.15 Assessment of Effect on Growth

- There was no assessment of growth that would not be expected in a study of predominantly of adults who were no longer growing.

7.1.16 Overdose Experience

- There was no assessment of this topic.

7.1.17 Postmarketing Experience

The sponsor noted that the safety of lamotrigine is reviewed on an ongoing basis by the Global Clinical Safety and Pharmacovigilance (GCSP) department at GSK. It is GSK policy to review all incoming AE reports from all sources including clinical trials, spontaneous reports, regulatory authorities, published literature and from post-marketing surveillance studies. These data are further analyzed in a cumulative setting to identify any potential new safety signals. Any adverse drug reactions identified are then incorporated into the GSK

Global Data Sheet and local prescribing information.

Lamotrigine (LAMICTAL) immediate-release (IR) tablet was first approved on 05 November 1990 in Ireland and is now available in over 100 countries. Exposure to lamotrigine is extensive following over 15 years of market experience and the AE profile is well characterized. The

cumulative world-wide exposure to lamotrigine (all indications) from launch up to 31 May 2006 is approximately 6.9 million patient-years.

This estimate is based on the available sales volume data, from the Intercontinental Medical Statistics database MIDAS.

The GSK Clinical Safety database was searched up to 28 June 2006 to identify all spontaneous (healthcare professional, consumer, regulatory authorities) and published literature reports, where lamotrigine was reported as a suspect drug, in the following four categories :
• Death reports
• All SAE reports
• Reports of serious skin rash
• Reports of multi-organ failure

The sponsor summarized this post-marketing information.

In summary, the sponsor noted that the information included in the lamotrigine Global Data Sheet and the US prescribing information reflects the post-marketing experience with lamotrigine to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Section 4.1 shows the various studies that were used to support this NDA. In addition, open-label experience from study 36 (assessing the effect of XR lamotrigine on the control of Primary Generalized Tonic-Clonic Seizures in adults) was used along with blinded data (placebo and XR) from the randomized, double-blinded, placebo-controlled study phase.

7.2.1.2 Demographics

The demographic characteristics for the patients in studies 34 and 36 are shown in Table 61. This table shows that most patients were between the ages of 16-65, the distribution between gender was similar, and the vast majority of patients studied were Caucasian.

Table 61 Demographic Characteristics (Studies LAM100034 and LAM100036-Combined)

	Number (%) of Subjects[a,b]			
	LAM100034 Double-Blind Treatment Phase		LAM100036	LAM100034 and LAM100036 Combined
	Placebo N=120	LTG XR N=116	Blinded Data N=72	LTG XR N=311
Age (mos)				
Mean (SD)	37.5 (14.40)	35.8 (12.68)	31.6 (11.46)	36.0 (13.54)
Median	36.0	35.0	29.5	35.0
Range	14-73	13-70	15-61	13-73
Age Stratum, n (%)				
<16 years	4 (3)	5 (4)	2 (3)	13 (4)
16-65 years	112 (93)	108 (93)	70 (97)	289 (93)
>65 years	4 (3)	3 (3)	0	9 (3)
Sex, n (%)				
Female	57 (48)	62 (53)	36 (50)	148 (48)
Male	63 (53)	54 (47)	36 (50)	163 (52)
Race, n (%)				
African American/African Heritage	10 (8)	3 (3)	3 (4)	17 (5)
American Indian or Alaskan Native	3 (3)	4 (3)	0	6 (2)
Asian - Central/South Asian Heritage	9 (8)	16 (14)	25 (35)	57 (18)
Asian - East Asian Heritage	14 (12)	15 (13)	1 (1)	30 (10)
Asian - Japanese Heritage	0	0	1 (1)	0
Asian - South East Asian Heritage	2 (2)	0	0	2 (<1)
White - White/ Caucasian/ European Heritage	83 (69)	77 (67)	43 (60)	199 (64)

Data Source: Table 5.12, Table 5.13, Table 5.16, Table 5.17; LAM100034 CSR, Table 6.7 and Table 6.8
a. ITT Population during the Double-Blind Treatment Phase of study LAM100034.
b. Safety Population in LAM100036 blinded subjects and unblinded subjects in LAM100034 and LAM100036 combined.

In study LEP103944 (the relatively short-term study providing the PK and safety experience of patients from converting from a dose of IR to XR), subjects were predominantly not of Hispanic/Latino ethnicity(89%) and White (98%) (LEP103944 CSR, Section 6.4.1). There were more female subjects (57%) than male subjects (43%). The median age of subjects was 38.5 years with a range of 18 to 88 years.

7.2.1.3 Extent of exposure (dose/duration)

In response to my inquiries, the sponsor submitted several tabular summaries of exposure relate to dose and duration. Table 62 summarizes the long- term safety exposure for all patients according to modal, total daily XR dose. Table 63 shows the long-term exposure relative to age and gender.

Table 62 Summary of Long-Term Exposure to XR Lamotrigine for Modal Dose for Any Dose and Various Total Daily Dose Ranges for Patients in Studies 34 (DBP and OLP) and 36 (OLP)

Duration of exposure to study drug	<300 mg/d (N=108)	>=300 to <500 mg/d (N=82)	>=500 mg/d (N=130)	Total (N=320)
< 26 weeks	65 (60.2%)	31 (37.8%)	47 (36.2%)	143 (44.7%)
>= 26 weeks	43 (39.8%)	51 (62.2%)	83 (63.8%)	177 (55.3%)
>= 52 weeks	6 (5.6%)	6 (7.3%)	17 (13.1%)	29 (9.1%)
Any Exposure	108 (100.0%)	82 (100.0%)	130 (100.0%)	320 (100.0%)

Table 63 Summary of Long-Term Exposure to XR Lamotrigine According to Age and Gender for Patients in Studies 34 (DBP and OLP) and 36 (OLP)

Exposure to at Least Week (t)	Total Subjects	Gender: Male	Gender: Female	Age at Screen: <16	Age at Screen: 16-65	Age at Screen: >65
< 26	228	121	107	11	209	8
>=26	83	42	41	2	80	1
>=52	13	6	7	1	12	0

Table 64 shows the number of patients according to the modal, total daily for completers and patients discontinuing prematurely (patients could have used this modal dose for any duration of time in the study). A relatively small number of patients received a total daily XR dose of 600 mg in the DBP and for prolonged treatment (Table 65). Only 11 patients received a modal daily dose of 600 mg for prolonged periods of $\geq$ 26 weeks and two of these received treatment for $\geq$ 52 weeks. In addition, 3 patients received higher daily doses above 600 mg (e.g. 800-1000 mg) for $\geq$ 26 weeks. Table 66 shows that most of these patients were receiving concomitant EIAEDs (with or without "neutral" AEDs). None of these long-term exposure patients were using VPA and a few were using "neutral" AEDs.

Table 64 Summary of Modal (for Any Exposure Time) Total Daily XR Lamotrigine Dosing in Study 34 (DBP)

Dose (mg/day)	Lamictal-XR VPA alone (N=24)	Lamictal-XR VPA with EIAEDs (N=7)	Lamictal-XR EIAEDs (N=60)	Lamictal-XR All other regimens (N=27)	Lamictal-XR ALL (N=118)
0 (really 50)	0	0	1	0	1
12.5	2	0	0	0	2
25	2	1	0	0	3
50	0	0	4	2	6
100	0	0	2	1	3
150	1	0	0	0	1
200	17	3	0	0	20
250	2	0	0	0	2
300	0	0	0	23	23
400	0	1	4	1	6
450	0	0	2	0	2
500	0	1	42	0	43
600	0	1	5	0	6

Table 65 Summary of XR Lamotrigine Long-Term Exposure for "High" Modal Doses (≥ 500 mg/d) for Patients in Study 34 (DBP and OLP) and Study 36 (OLP)

AEDType: Total

Duration of exposure to study drug	500 mg/d	525 mg/d	550 mg/d	600 mg/d	700 mg/d	800 mg/d	900 mg/d	1000 mg/d	Total
N=	92	2	4	27	2	1	1	1	130
< 26 weeks	24(26%)	2(100%)	3(75%)	16(59%)	2(100%)	0(0%)	0(0%)	0(0%)	47(36%)
>=26 weeks	68(74%)	0(0%)	1(25%)	11(41%)	0(0%)	1(100%)	1(100%)	1(100%)	83(64%)
>=52 weeks	14(15%)	0(0%)	0(0%)	2(7%)	0(0%)	1(100%)	0(0%)	0(0%)	17(13%)
Any Exposure	92(100%)	2(100%)	4(100%)	27(100%)	2(100%)	1(100%)	1(100%)	1(100%)	130(100%)

Table 66 Summary of XR Lamotrigine Long-Term Exposure for "High" Modal Doses (≥ 500 mg/d) for Patients Using EIAEDs (with or without "neutral" AEDs) in Study 34 (DBP and OLP) and Study 36 (OLP)

AEDType: EIAEDs alone or with non-inducing/inhibiting AEDs

Duration of exposure to study drug	500 mg/d	525 mg/d	550 mg/d	600 mg/d	700 mg/d	800 mg/d	900 mg/d	1000 mg/d	Total
N=	87	2	4	24	1	0	1	1	120
< 26 weeks	23(26%)	2(100%)	3(75%)	14(58%)	1(100%)	0(0%)	0(0%)	0(0%)	43(36%)
>=26 weeks	64(74%)	0(0%)	1(25%)	10(42%)	0(0%)	0(0%)	1(100%)	1(100%)	77(64%)
>=52 weeks	13(15%)	0(0%)	0(0%)	1(4%)	0(0%)	0(0%)	0(0%)	0(0%)	14(12%)
Any Exposure	87(100%)	2(100%)	4(100%)	24(100%)	1(100%)	0(0%)	1(100%)	1(100%)	120(100%)

Reviewer Comment

- A relatively large number (N=177) of patients were exposed to the XR formulation for at least 26 week/6 months (Table 62). A much smaller, but considerable number (N=29) were exposed to this new formulation for at least 52 weeks/12 months. In addition, a considerable percentage (~ 50 %) of these patients were treated with ≥ 500 mg daily as a modal dose (and most of these exposures were = 500 mg/d).

- Long-term exposure to young (< 16 years) and "elderly" (> 65 years) was virtually absent with only 2 young patients being treated for at least 26 weeks (N=1 for ≥ 52 weeks) and one 1 "elderly" patient being treated for at least 26 weeks (none for ≥ 52 weeks). The virtual absence of long-term exposure in young patients does not support labeling this treatment for patents below 16 years. The absence of long-term safety experience exposure in "elderly" patients may warrant mention in the label.

- The long-term safety experience treatment is limited at the 600 mg daily dosing level. However, considering that : 1) the mean AUC of XR lamotrigine is approximately 80 % of that of the IR formulation in patients taking EIAEDs alone or with "neutral" concomitant AEDs; 2) most long-term treatment patients were using EIAEDs; and 3) IR lamotrigine is labeled to use up to 500 mg daily in patients taking EIAEDs, it seems reasonable to allow the 600 mg dose for patients using EIAEDs alone or with "neutral" AEDs. Considering the lower bioavailability of the XR formulation with that of the IR formulation, a 600 mg XR dose would approach a 500 mg IR dose (e.g. 0.8 X 600 mg = 480 mg).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

- Not applicable

7.2.2.2 Postmarketing experience

See section 7.1.17 Postmarketing Experience

7.2.2.3 Literature

- The sponsor did not present a literature review.

7.2.3 Adequacy of Overall Clinical Experience

Reviewer Comment

- Overall, the total and long-term safety exposure is probably sufficient. The total number of exposures and the long-term exposures for ≥ 26 weeks, and for ≥ 52 weeks/12 months are below the ICH guidelines of 1500, 300, and 100 respectively. The total number of exposures in the single dose (N=184) and the multiple dose (N=41) Clinical Pharmacology studies and the clinical studies (N=311) for which safety has been collected is slightly above 500 patients. The total number of at least 6 and 12 month long-term exposures is 177 and 29 patients, respectively. However, the ICH guidelines are more typically applied to a New Molecular Entity (NME) and XR lamotrigine is a new formulation of a product (IR lamotrigine) that has been in use for many years and has been administered to a large number of patients in different population at different doses for different periods (including long-term treatment).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- Not applicable

7.2.5 Adequacy of Routine Clinical Testing

Reviewer Comment

- Although the routine clinical testing in the controlled study 34 was adequate, the sponsor limited its safety data collection in its 2 open-label, extension studies (34 and 36) to solely TEAEs. More specifically, the sponsor did not collect safety data for VS, ECGs, or clinical laboratory analytes in these OL extension/continuation study phases.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Reviewer Comment

- The Clinical Pharmacology review thought that this was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug;Recommendations for Further Study

Reviewer Comment

- This evaluation appears to be adequate.

7.2.8 Assessment of Quality and Completeness of Data

Reviewer Comment

- Overall, the quality of the data appeared to be reasonable based upon what was submitted originally by the sponsor or in response to my requests. However, in many instances the sponsor's analyses were not optimally probing and/or did not appear to be complete in regard to spontaneous submission by the sponsor with the original NDA. In some instances, the sponsor submitted data/information/analyses that had not been submitted in response to my inquiries/requests.
- The DSI inspections (planned just prior to the PDUFA action date) are pending and at least preliminary reports of these inspections at 2 sites in Seoul, Korea is expected prior to the PDUFA action date.

  However, internal, quality control inspections of both of these Korean sites by the sponsor suggested many errors in transcription of source data to CRFs (see section 4.4 Data Quality and Integrity).

7.2.9 Additional Submissions, Including Safety Update

SYNOPSIS

Overview
This 120-day Safety Update report updates the safety profile for lamotrigine extended release (XR) tablets by summarizing information available since the cut-off date for safety information in NDA 22-115 (28 June 2006) through the cut-off date of 31 October 2006. **This report includes safety information from two completed clinical pharmacology studies and three ongoing clinical studies**.

Clinical Pharmacology Studies
Data from two completed studies are included in this 120-day update. Both were conducted in healthy subjects. SCA104648 was a placebo-controlled repeat-dose/multidose study to evaluate the effect of lamotrigine at doses up to 400mg/day on QT/QTc interval, incorporating moxifloxacin as a positive control. Although it was conducted with an immediate release (IR) formulation of lamotrigine, GSK considers this information relevant to the extended-release formulation. LAM105377 was a pharmacokinetic study which compared the bioavailability of three, prototype, 300mg enteric coated, modified release tablet formulations of lamotrigine administered as a single dose with a reference single dose of 300mg dose of lamotrigine comprised of one 200mg lamotrigine XR tablet plus one 100mg lamotrigine XR tablet.

SCA104648
In SCA104648, the overall frequency of AEs was similar for moxifloxacin and its placebo in the single-blind, cross-over phase, although headache, nausea, dizziness and diarrhea were more frequent on moxifloxacin. During the double-blind, parallel group phase with lamotrigine or placebo, the frequency of AEs on lamotrigine was similar to placebo during the 25mg, 50mg, 100mg and 200mg/day dosing periods. At the 300mg and 400mg/day dose levels, AEs were more frequent on lamotrigine than the corresponding placebo period (29% compared with 13% at the 300mg/day dose and 47% compared with 37% at the 400mg/day dose level). The highest frequency of AEs was observed at the highest lamotrigine dose (400mg/day). The most common

adverse events in this study were consistent with those seen in earlier clinical pharmacology studies with lamotrigine (headache, dizziness, nausea) and summarized in previous applications, including NDA 22-115.

One SAE was reported by Subject 800125 in study SCA104648 and was included in the initial submission of NDA 22-115. This was pulmonary tuberculosis of severe intensity while the subject was taking placebo. There were no additional SAEs during the reporting period and there were no deaths in this study. As reported in NDA 22-115, 12 subjects were withdrawn from study SCA104648 due to AEs, of whom four were withdrawn due to drug-related AEs during the lamotrigine dosing period: two due to rash or drug eruption, one due to raised ALT/AST, and one due to collapse, abdominal pain, sweating and dyspnea. Rash also led to the withdrawal of two subjects after moxifloxacin single dose and one on placebo. There were no additional withdrawals due to AEs during the reporting period.

The sponsor noted that no prolongation of QTcF or QTcB interval was observed in healthy volunteers at steady state 100mg, 300mg or 400mg/day lamotrigine IR compared with placebo. The PK/PD model indicated that there was a statistically significant decrease in individually corrected QT intervals for lamotrigine and a statistically significant increase in individually corrected QT intervals for moxifloxacin over the respective concentration ranges studied.

LAM105377
In LAM105377, overall, the highest proportion of subjects reporting AEs was seen on the reference formulation (Treatment Group A), with 53% of subjects reporting AEs, whereas 33% to 43% of subjects on the prototype formulations reported AEs. The most frequently-reported AE was headache, but this was only reported by more than one subject in Treatment Groups A and B (reference formulation and prototype formulation 1). Nausea was reported by 2 subjects (14%) in Treatment Group B (formulation 1) but in no other treatment groups. Hot flush was reported by 3 subjects (20%) in Treatment Group D (formulation 3) but in no other treatment groups. Petechiae and erythematous rash AEs were each reported by one subject, in different treatment groups. Both of these AEs were of a mild intensity and neither was considered by the investigator to be related to study drug.

No SAEs, deaths, or withdrawals due to AEs were reported in study LAM105377.

Clinical Studies
No additional clinical studies completed during the reporting period.

Safety Information from Studies in Progress
Clinical Pharmacology
As of the data cut-off date, there were no ongoing clinical pharmacology studies.

Clinical Studies
Safety data from the following three ongoing clinical studies are included in this update: LAM100034 Continuation Phase (adjunctive therapy of partial epilepsy), LAM100036 (blinded data from the Double-Blind Treatment Phase and unblinded data from the Continuation Phase

(adjunctive therapy of PGTC epilepsy), and LAM30055 (open-label, historical-controlled study evaluating conversion to monotherapy with lamotrigine XR in adult- ≥ 13 yr old patients with partial seizures receiving therapy with a single AED). **As these three studies are ongoing, available data were limited to deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) for the reporting period 29 June 2006 to 31 October 2006**.

An open-label, historical-controlled study (LAM30055) evaluating conversion to monotherapy with lamotrigine XR in adult (≥13 years old) subjects with partial seizures receiving therapy with a single antiepileptic drug (AED).

There were a total of 25 new subject exposures to lamotrigine XR during this reporting period plus the additional 11 new subject exposures to blinded study drug (lamotrigine XR or placebo) in the Double-Blind Treatment Phase of LAM100036.

The initial NDA 22-115 submission included an integrated analysis of SAEs from the Double-Blind and Continuation Phases of study LAM100034 and the Continuation Phase of Study LAM100036 (unblinded subjects). At that time, the overall incidence of SAEs for these unblinded subjects was 4% (13/311 subjects). At the data cut-off date for this safety update, the cumulative incidence of SAEs for LAM100034 and the Continuation Phase of LAM100036 was 7% (21/320 subjects).

There were no new fatal SAEs during this reporting period. However, there was an update to the fatal SAE term for one subject enrolled in study LAM100034 (Subject 2152) whose death was reported previously in NDA 22-115. The investigator clarified that the cause of death for Subject 2152 was drug toxicity which the investigator believes may have been caused by study drug.

There were 16 additional treatment-emergent non-fatal SAEs reported for ten subjects during the reporting period. Seven of the subjects experiencing SAEs were in the Continuation Phase of study LAM100034; two subjects were in the Continuation Phase of study LAM100036, and one subject was in the Double-Blind Treatment Phase of study LAM100036. There were no SAEs that occurred in more than one subject. Three SAEs (dysarthria, vomiting, coordination abnormal) for one subject were considered to be related to study drug. None of the subjects withdrew from a study due to the SAE.

A total of seven subjects withdrew from a clinical study in progress due to an adverse event during the reporting period: six subjects in the Continuation Phase of LAM100034 and one subject in LAM100036 (Double-Blind Treatment Phase). The AEs leading to withdrawal were not serious and all were considered by the investigator to be related to study drug. The six subjects in LAM100034 had all been previously randomized to placebo in the Double-Blind Treatment Phase and were receiving adjunctive treatment with lamotrigine XR in the Continuation Phase when they withdrew from the study. Two subjects discontinued a clinical study due to rash (one each in LAM100034 and LAM100036). In addition, there was an update to the AE term (changed from sudden death to drug toxicity) for one subject enrolled in study LAM100034 (Subject 2152) whose withdrawal due to an SAE was reported previously in NDA

22-115. While there were no new reports of pregnancy during the reporting period, one pregnancy did occur in study LAM100036 after the 31 October 2006 data cut-off date. The outcome of this pregnancy is not currently known.

Post-Marketing Data
The GSK Clinical Safety database was searched from 29 June 2006 to 31 October 2006 to identify all spontaneous (healthcare professional, consumer, regulatory authorities) and published literature reports, where lamotrigine was reported as a suspect drug, in the following four categories :

• Death reports
• All Serious Adverse Event (SAE) reports
• Reports of serious skin rash
• Reports of multi-organ failure

The search identified a total of 31 reports documenting a patient with a fatal outcome.
There were a total of 442 SAE reports documenting a total of 1721 events most of which fell into the MedDRA System Organ Class (SOC) of Skin and subcutaneous tissue disorder (344 events), Nervous system disorders (243), Psychiatric disorders (180), General disorders and administration site conditions (177), and Gastrointestinal disorders (131).

Two separate searches of the Clinical Safety database were performed to identify reports of serious skin rash. One search utilized the Standardized MedDRA Query (SMQ) for severe cutaneous adverse reaction (Version 9.1), and the second involves selecting all the relevant rash event terms.

The search using the term severe cutaneous reaction identified a total of 106 reports.
The second search identified reports meeting FDA seriousness criteria and the following MedDRA terms :
MedDRA higher level terms: bullous conditions, dermatitis and eczema, exfoliative conditions, rash, eruptions and exanthems.
MedDRA preferred terms: skin lesion, skin necrosis, skin reaction, epidermal necrosis, skin toxicity, drug eruption, toxic skin eruption, erythema, rash erythematous, generalized erythema, rash papular, rash papulosquamous, rash follicular, acute generalized exanthematous putulosis, skin erosion, skin ulcer, vasculitic rash, systemic lupus erythematosus rash.

This search retrieved a total of 141 reports.

The database was searched for all reports of lamotrigine with events that coded to the MedDRA preferred term of multi-organ failure. The search identified one report.

Sponsor's Conclusions
During this update period, the additional clinical pharmacology data and data from clinical trials continue to support the acceptability of the safety and tolerability of lamotrigine XR as presented in NDA 22-115. These new data have no impact on the

proposed labelling submitted with the application.

Reviewer Comment

- I agree that the information presented in the 4 MSU did not suggest a different impression of the safety profile of XR than had been suggested based upon the original NDA submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The sponsor pooled TEAE safety data in the DBP and OLP of study 34 along with TEAEs in the OLP of study 36.

Reviewer Comment

- I did not think that pooling all these data was very helpful in providing any insight compared to that obtained from review of the DBP of study 34.

7.4.1.2 Combining data

- See section 7.4.1.1

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Reviewer Comment

- The sponsor did not originally conduct analyses assessing for dose-dependent TEAE findings of XR lamotrigine associated with different total dosing per se. This may be because the sponsor thought that randomization to different, daily target doses (i.e. 200, 300, or 500 mg) based upon concomitant AED grouping/class was expected to result in similar PK exposures. Patients randomized to 500 mg were on an EIAED that could

reduce AUC exposure by ~ 50 % and those randomized to 200 mg were on VPA that could increase AUC exposure by ~ 100 %. However, in response to my request, the sponsor did conduct TEAE analyses according to 3 different, daily dose ranges (< 300 mg, 300 - < 500 mg, and ≥ 500 mg, and the dose at the time of TEAE onset). Overall, these analyses did not suggest much dose-dependence of TEAEs (see section 7.1.4 Other Search Strategies).

7.4.2.2 Explorations for time dependency for adverse findings

Reviewer Comment

- The sponsor did not conduct any exploratory analyses assessing for time-dependent effects of lamotrigine. However, in response to my requests, the sponsor conducted analyses of TEAEs investigating the number and incidence of TEAEs with onset in the titration/escalation phase, in the maintenance phase, in either titration and/or maintenance phase, and for TEAEs with onset in the titration phase "persisting" (≥ 7 days) into the maintenance phase. Results of these analyses, that provided some potentially valuable insight into a better understanding of TEAEs, are presented and discussed in section 7.1.4 Other Search Strategies.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor conducted analyses of TEAEs according to gender, age, and race.

The sponsor noted that female subjects in both treatment groups generally reported TEAEs more frequently than male subjects and that were slight differences between males and females with the events nausea and dizziness.

Because there were so few subjects in the group aged 65 years or older (7/236, 3%), comparisons by age group were not informative.

While most of the race groups had too few subjects to make informative comparisons, a greater percentage of East Asian subjects in the LTG XR group (8/15, 53%) experienced dizziness compared with East Asian subjects in the placebo group (0/14 subjects). A post-hoc analysis of most common TEAEs by country was performed. While most of the country groups had too few subjects to make informative comparisons, a greater percentage of Korean subjects in the LTG XR group (8/15, 53%) experienced dizziness compared with Korean subjects in the placebo group (0/16 subjects).

7.4.2.4 Explorations for drug-disease interactions

The sponsor did not present any explorations of drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

The sponsor noted that most of the AED groups had too few subjects to make informative comparisons regarding notable or substantially different risks for TEAEs according to

7.4.3 Causality Determination

TEAEs judged by the investigator to be at least reasonably attributable to study drug are presented in Table 67. TEAEs were judged by the investigator to be attributable to study drug in 23 (19%) subjects in the placebo group and 42 (36%) subjects in the LTG XR treatment group; dizziness was judged by the investigator to be attributable to study drug in the LTG XR group for 17 (14%) subjects.

Table 67 Adverse Events Considered Being Reasonably Attributable to Study Drug Reported in Greater Than or Equal to 5% of Subjects in Either Treatment Group (Safety Population: Study LAM100034)

System Organ Class Preferred Term	Number (%) of Subjects	
	PBO N=121	LTG XR N=118
Any Event	23 (19)	42 (36)
Dizziness	2 (2)	17 (14)
Headache	4 (3)	8 (7)
Somnolence	3 (2)	6 (5)

Data Source: Table 8.15

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor's proposed dosing regimen for the label is shown in Table 68.

Table 68 Sponsor's Proposed Dosing Regimen for the Label

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day

(b) (4)

* Rifampin and estrogen-containing estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

Reviewer Comment

- The proposed dosing regimen is the one used in clinical study 34. Although the target daily dose was 200, 300, and 500 mg for concomitant VPA, "neutral" AEDs, and EIAEDs, the protocol allowed for reducing the dose for problems with tolerability/TEAEs, and for increasing the dose to 250, 400, and 600 mg respectively for inadequate seizure control.

- The long-term safety experience treatment is limited at the 600 mg daily dosing level. However, considering that : 1) the mean AUC of XR lamotrigine is approximately 80 % of that of the IR formulation in patients taking EIAEDs alone or with "neutral" concomitant AEDs; 2) most long-term treatment patients were using EIAEDs; and 3) IR lamotrigine is labeled to use up to 500 mg daily in patients taking EIAEDs, it seems reasonable to allow the 600 mg dose for patients using EIAEDs alone or with "neutral" AEDs. Considering the lower bioavailability of the XR formulation with that of the IR formulation, a 600 mg XR dose would approach a 500 mg IR dose (e.g. 0.8 X 600 mg = 480 mg). Thus, the 600 mg daily dosing of XR seems justified and reasonable in patients also taking a concomitant EIAED. Six of the randomized patients appeared to use a 600 mg daily dose.

- In contrast. I do not believe that the 150 mg daily dose of XR is justified for inclusion in the dosing recommendation in the label for a patient using VPA. Only 1 patient in the randomized treatment group used 150 mg XR daily. Thus, there is an insufficient number of patients who had been treated with this dose to justify this lowest dose in the labeled recommendation for dosing. The lowest recommended dose should be 200 mg daily, a

dose at which many patients on VPA had been studied and included in the primary analysis of the primary efficacy endpoint.

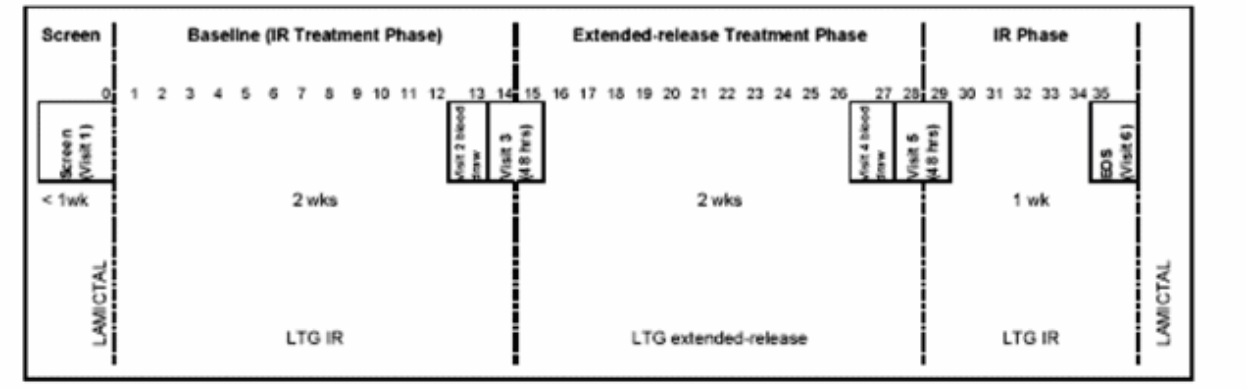
Study LEP103944 Showing The Pharmacokinetics and Safety of Converting from IR Lamotrigine to XR Lamotrigine

LEP103944 was an open-label study designed to characterize the pharmacokinetic (PK) profile of lamotrigine when administered as extended-release once daily compared to the current formulation (lamotrigine IR) administered twice daily. The double-conversion study had three phases after screening: a baseline with lamotrigine IR, a treatment phase with lamotrigine XR and a last phase with lamotrigine IR. More specifically, PK assessments were conducted at steady-state following administration of lamotrigine IR bid (Day 14), on the first day of switching to the lamotrigine XR formulation od (Day 15), and then at steady-state for the XR formulation od (Day 28). The following day (Day 29), patients were switched back to their lamotrigine IR regimen using the same daily dose, and intense pharmacokinetic sampling was again conducted. The schematic of the study design is shown in Figure 9.

The relative bioavailability of XR and IR was studied based on three categories of concurrent antiepileptic drug(s) (AED) treatment :

- Group 1 ("Neutral" group): subjects taking LTG IR monotherapy or lamotrigine LTG IR with a non-inducing, non-inhibiting AED.
- Group 2 (Induced group): subjects taking LTG IR and an inducing AED (with or without a "neutral" AED).
- Group 3 (Inhibited group): subjects taking LTG IR and VPA (with or without a "neutral" AED).

Figure 9 Schematic of the Design for "Conversion" Study LEP103944



Descriptive summary statistics are shown for total, daily IR lamotrigine dose are shown in Table 69.

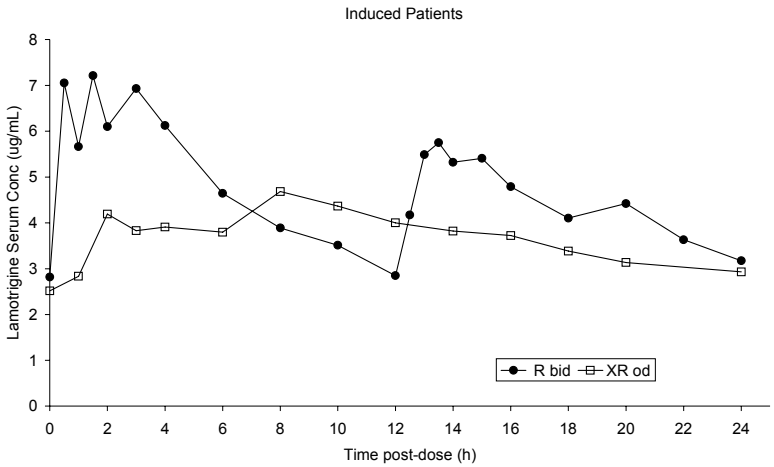
Table 69 Summary of AED Group Data for Lamotrigine Daily Dosing in Study LEP103944

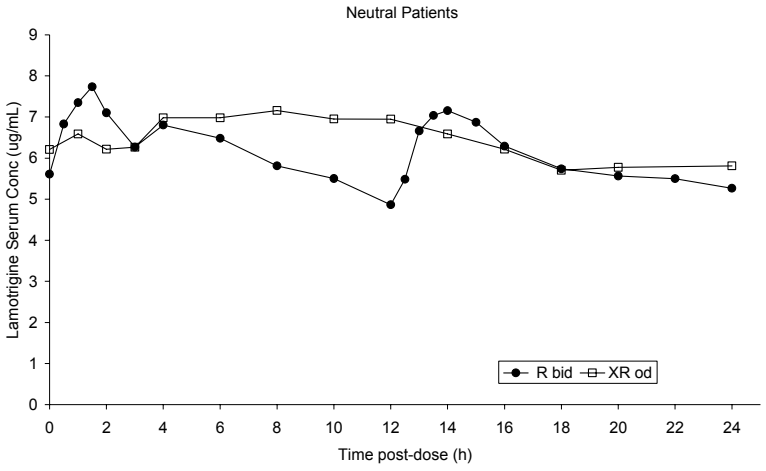
		Average Dose of LAMICTAL (mg)			
Dosing Group	n	Mean	Median	Min	Max
Group 1: Neutral	15	363.3	400.0	200	600
Group 2: Induced	15	550.0	600.0	200	1200
Group 3: Inhibited	14	282.1	200.0	50	800

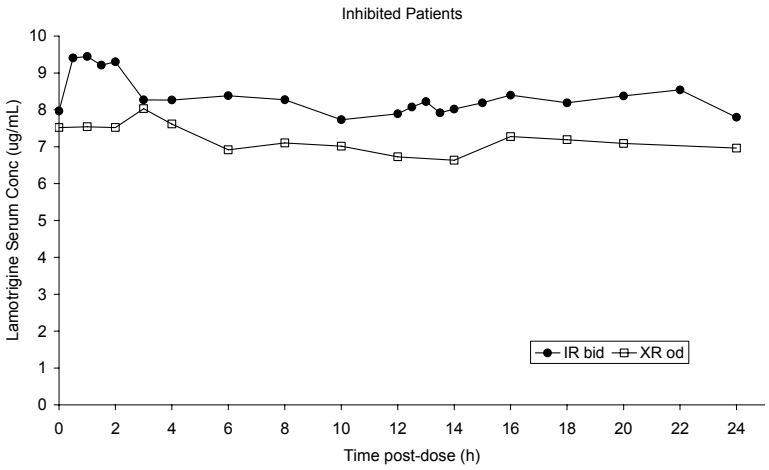
Source Data: Table 8.1

Median plasma lamotrigine time profiles (at PK steady-state) are shown for IR vs XR lamotrigine administration according to each AED group in Table 70.

Table 70 Median Serum Lamotrigine Concentration-Time Profiles for Steady-State IR and Steady State XR for each AED Group







The rate of absorption of lamotrigine was slower following administration of lamotrigine XR compared to lamotrigine IR. In each of the three groups, the median time to Cmax following administration of lamotrigine IR was between 1 and 1.5 hours post-dose, whereas, following administration of lamotrigine XR, the median time to Cmax was increased to 4 – 6 h post-dose in the induced group, 6 – 10 h post-dose in the neutral group and 9 – 11 h post-dose in the inhibited group. Steady-state Cmax values were ~30% lower in the induced group and ~10% lower in the neutral and inhibited groups following administration of XR, compared to IR.

An assessment of the relative bioavailability of steady-state lamotrigine XR compared to lamotrigine IR (Day 28 vs. Day 14) was conducted using analysis of variance and is presented in Table 71.

Table 71 Adjusted Steady-State Geometric LS Mean Ratio and 90% CI of Dose Normalized Lamotrigine Steady-State PK Parameters XR vs. 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
$C\tau$/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

The overall relative bioavailability based on dose normalized AUC(0-24) following conversion from IR to XR at steady-state was estimated to be ~ 90%. For patients taking an EIAED, however, lower extent of lamotrigine systemic exposure (21% lower AUC and 29% lower Cmax) was observed with the XR formulation. reference formulation. For patients taking a "neutral" AED, differences between the extent of lamotrigine systemic exposure were minimal for XR vs IR formulations. For patients taking an inhibiting AED A(e.g. VPA), differences between the extent of lamotrigine systemic exposure were also minimal for XR vs IR.
In all three AED groups, similar or higher steady-state trough concentrations were observed on attainment of steady-state for the XR (Day 28) in comparison to the IR (Day 14).

Table 72 shows the PK comparisons immediately after switching from the IR to the ER dosage form.

Table 72 Statistical Summary of Serum LTG PK Parameters – Day 15 vs Day 14

Serum LTG PK Parameter	AED Group	Geometric LS Mean Ratio Extended Release (Day 15) / IR (Day 14)	90% CI
AUC(0-24) / Total Daily Dose	Overall	0.87	0.827, 0.908
	Induced	0.82	0.759, 0.896
	Inhibited	0.95	0.874, 1.032
	Neutral	0.83	0.770, 0.897
Cmax / Total Daily Dose	Overall	0.80	0.763, 0.837
	Induced	0.73	0.675, 0.799
	Inhibited	0.92	0.845, 0.993
	Neutral	0.76	0.702, 0.820

Immediately after the conversion from IR on Day 14 to XR formulation on Day 15, a comparable (about 5% reduction) total daily exposure in terms of dose-normalized AUC(0-24) was observed in subjects who were in the inhibiting AED group. For subjects taking inducing and neutral AEDs, a decrease in AUC(0-24) was observed with a mean decrease of 17% in subjects taking neutral AEDs and a mean decrease of 18% in subjects taking enzyme inducing AED. There was also a reduction in dose normalized mean Cmax in all three AED groups. There was a mean decrease of in Cmax of 8% in subjects who were taking inhibiting AEDs, 24% in neutrals and 27% in subjects taking enzyme inducing AEDs.

However, in these groups, there were some individuals who exhibited a notably greater reduction in Cmax and AUC immediately after converting from IR on day 14 to XR on the following day (day 15). The percent reduction in these outliers in each of these groups is shown in Table 73 based upon reviewing results of individual patient analyses conducted by Dr. Tandon, the primary Clinical Pharmacology reviewer. In addition, one patient on an EIAED showed a 3 fold increase in Cmax.

Table 73 Notably Reduced Outlier Cmax and/or AUC in Individual Patients for Conversion of IR (Day 14) to XR Lamotrigine (Day 15)

Group	% reduction in AUC(0-24)	% reduction in Cmax)
Inducers	53% (N=1)	41-60% (N=3)

	40% (N=2)	3-fold Increase (N=1)**
Neutrals	27-33%% (N=4)*	32% (N=4)*
Inhibitors	No change	No change

*This is within the intersubject variability ** one subject in the Inducer group had a 3-fold higher Cmax

In addition, there were some individuals who also exhibited a notably reduced Cmax and/or AUC **two weeks after conversion from IR to XR**. The percent reduction in these outliers in each of these groups is shown in Table 74.

Table 74 Notably Reduced Outlier Cmax and/or AUC in Individual Patients for Conversion of IR (Day 14) to XR Lamotrigine (Day 28, after 2 weeks conversion)

Group	% reduction in AUC(0-24)	% reduction in Cmax)
Inducers	57-70% (N=2) 29% (N=1)*	45-77% (N=3)
Neutrals	27% (N=1)*	30% (N=1)*
Inhibitors	70% (N=1)**	70% (N=1)**

*these are still within the inter-subject variability seen with lamotrigine (i.e. up to 40% variability seen in other studies)

**This subject has a reduction in exposure even on converting back to the IR treatment on Day 29, hence this reduction could be due to some other reason that could not be determined.

The Clinical Pharmacology reviewer, Dr. Tandon, emphasized that these analyses show that, some patients (especially those in the EIAED Group) may have much lower levels (Cmax and/or AUC) in the XR lamotrigine levels. These reduced plasma lamotrigine levels may not only occur immediately after switching from IR to XR but also after a sustained time (e.g. 2 weeks) after switching. Dr. Tandon further noted that the therapeutic response in these groups may be different and she recommends that patients who convert from IR to XR should be monitored for appropriate dose adjustment as needed based upon seizure control after switching.

Table 75 presents summary statistics of the derived steady-state plasma lamotrigine PK parameters, separated by AED group.

Table 75 Steady-State Lamotrigine (IR vs XR) Pharmacokinetic Parameters for Geometric Mean (CV%)

	Day	N	AUC(0-24) (ug.h/mL)	Cmax (ug/mL)	Cmin (ug/mL)	FI[a]	Tmax (h)[b]
Induced							
IR	14	12	100 (85.9%)	6.71 (80.5%)	2.66 (100%)	0.99 (40.1%)	1.01 (0.5–2.98)
XR	28	12	79.0 (100%)	4.77 (85.9%)	2.10 (131%)	0.82 (50.0%)	4.00 (0.00–24.0)
Neutral							
IR	14	14	142 (43.4%)	7.82 (39.3%)	4.57 (46.6%)	0.55 (29.5%)	1.50 (0.5–3.02)
XR	28	13	138 (40.8%)	6.83 (38.6%)	4.87 (41.0%)	0.34 (40.6%)	6.00 (0.00–24.0)
Inhibited							
IR	14	12	208 (59.7%)	10.2 (57.5%)	7.43 (53.9%)	0.32 (27.0%)	1.00 (0.50–6.13)
XR	28	10	167 (48.1%)	7.77 (49.0%)	6.31 (47.1%)	0.21 (16.4%)	11.0 (0.00–24.0)

[a] FI = Fluctuation Index = (Cmax-Cmin)/Cavg
[b] presented as median (range)

Clinical Pharmacology Review Summary of Findings for PK Comparisons and Conversion from IR to XR lamotrigine

The PK comparisons on switching from the lamotrigine IR to the XR dosage form in patients was done in the presence of 3 concomitant AED groups (inducers, inhibitors and "neutrals") in a study with approximately 12 subjects in each group. These comparisons showed the following findings :

- The steady-state trough concentrations for Lamotrigine XR were either 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 depending on concomitant AED, however some subjects on enzyme inducing AED had reduction in Cmax of 45-77% (N=3) as well. In general the lower Cmax with extended release formulation resulted in a decrease of peak to trough fluctuation in serum lamotrigine concentrations.

- The mean 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 approximately similar (6% decrease) with respect AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR based on means. However some subjects (N=2) on EIAEDS had a 57-70% reduction in AUC(0-24ss). **Therefore, these subjects may not have the same therapeutic response on conversion to the XR formulation, dose may need to be titrated to therapeutic response**.

Sponsor's Summary of Efficacy and Safety During Study LEP103944

It is important to recall that study LEP103944 was conducted under open-label conditions. The sponsor noted that weekly seizure control did not seem to change in during conversion and that the majority of investigators assessed the subjects' seizure frequency as "approximately as expected" during all treatment phases.

The sponsor also noted that safety and tolerability of XR QD was comparable to that of IR BID.

Sponsor Recommendations

The sponsor recommends that patients may be converted directly from IR lamotrigine to XR and that the initial dose of XR should match the total daily dose of IR on the previous day. The sponsor also notes that after conversion, the XR dose may be adjusted depending on therapeutic response.

Reviewer Comment

- Overall, PK results for Cmax, and/or AUC appear to be either similar or reduced after converting from the same total daily dose of IR to XR. In general, the magnitude of the reduction seems to depend on the concomitant AED group (i.e. inhibitor, inducer, neutral) with patients on an EIAED seeming to have the greatest risk for reduced PK levels. Of potential importance, some individual patients (especially those on an EIAED) can have notably reduced plasma lamotrigine levels not only immediately after switching from IR to XR but also at 2 weeks after conversion. If conversion is permitted in the label, the language should clearly emphasize that it is not known if seizure control will be similar with XR as it was with IR and that patients should be monitored for possible dose adjustment based upon not only seizure control but also tolerability.

- The TEAE safety experience after switching from IR to XR generally appeared similar with the exception that the incidence of headache increased to 21 % while on XR (vs 11 % on IR) and decreased to 3 % after switching back to IR.

- Of interest, the incidence of vital sign outliers (based upon my requested analyses) with moderately decreased ($\geq$ 20 mm Hg) diastolic blood pressure increased to 14 % while on XR for 2 weeks (vs 5 % on IR for 2 weeks) and decreased to 12 % after switching back to IR for 1 week. In addition, the incidence of outlier patients with an increase ($\geq$ 15 BPM) in pulse increased to 6 % while on XR for 2 weeks (vs 0 % on IR for 2 weeks) and decreased to 3 % after switching back to IR for 1 week.

Food Interaction Study

In the clinical trials, XR lamotrigine was dosed without regards to food and this is the proposed dosing recommendation. Furthermore, a food interaction study did not suggest a significant effect of food that warrants inclusion in the label for restriction about dosing with meals.

Alcohol Interaction (Effect of ethanol on dissolution of XR Lamotrigine)

Ethanol did not have a significant impact on the release of XR lamotrigine tablets and there was no evidence of "dose dumping."

8.2 Drug-Drug Interactions

In addition to the results showing effects of concomitant AED on plasma lamotrigine, the sponsor conducted a drug-drug interaction (DDI) study assessing the effect of a proton pump inhibitor (esomeprazole), that reduces gastric acidity (i.e. increases gastric pH) on plasma lamotrigine in subjects administered XR lamotrigine.

Table 76 shows the effect of esomepreszole on Cmax and AUC. The median time to tmax was shorter when lamotrigine XR was administered with esomeprazole (~12 h) compared to administration of lamotrigine alone (~20 h). However, Cmax ranges was similar for the two regimens based on point estimates being close to unity (0.98) and the 90% CI (0.89, 1.08) being within the range associated with equivalence. The overall exposure to lamotrigine (AUC(0-∞)) was slightly lower (~12%) when lamotrigine XR was co-administered with esomeprazole.

Table 76 Point Estimates and 90% Confidence Interval (CI) for Bioavailability of 200 mg XR Lamotrigine in Presence or Absence of Esomeprazole (40 mg)

Parameter	Regimens	Ratio	90% CI
AUC(0-∞)	Esomeprazole : Placebo	0.88	(0.78, 1.00)
Cmax	Esomeprazole : Placebo	0.98	(0.89, 1.08)

These results indicate that rate of absorption is faster and the extent of absorption is decreased when lamotrigine XR is administered in a chronically increased gastric pH environment. Dr. Tandon, the Clinical Pharmacology reviewer, did not think the either of these findings would be clinically significant.

Reviewer Comment

- Major drug-drug interactions (DDIs) between IR lamotrigine and certain concomitant AEDs (e.g. EIAED that significantly reduces lamotrigine exposure and VPA that significantly increases lamotrigine exposure) are well known and sufficiently characterized. XR lamotrigine shows a similar DDI with these concomitant AEDs as does IR lamotrigine.

- A new study also showed that esomeprazole (proton pump inhibitor), that raises gastric pH slightly, lowers XR bioavailability (~ 12 % decreased AUC) by a small degree compared to that for IR lamotrigine. This relatively small effect is not likely to have an important clinical impact on most patients treated with XR lamotrigine. However, I am concerned that this DDI could potentially have a clinically significant impact on a

subgroup of certain patients (e.g. those using one or more concomitant EIAEDs). I noted this potential DDI interaction concern because EIAEDs have the potential for a considerable (~ 50 %) reduction in AUC on IR lamotrigine compared to patients not using EIAEDs and ~ a mean 21 % reduction of XR vs IR bioavailability. In addition, some individual patients using concomitant EIAEDs with XR lamotrigine have the potential for a much more marked decrease in bioavailability (vs IR) as reflected by a decrease in AUC up to ~ 50 % and decrease in Cmax up to ~ 60 %. I believe that a caution should be noted in the label that patients treated with XR lamotrigine and one or more concomitant EIAEDs in conjunction with a proton-pump inhibitor (or drug that can raise gastric pH) should be monitored to determine whether the dose of XR lamotrigine should be increased because of inadequate seizure control.

8.3 Special Populations

Reviewer Comment

- There are no comments here other than the facts that the label should note that XR is indicated for treatment of adult patients (≥ 16 years) with partial epilepsy and that there is little experience with treating elderly patients (> 65 years) with XR lamotrigine.

8.4 Pediatrics

Pediatric patients were not studied with the exception of a few patients (N=4 XR; N=3 Placebo) who ranged between 13-15 years old.

The Pre-NDA meeting minutes noted that : "GSK will need to submit a pediatric development plan with the NDA. If it is impossible to make an extended release tablet or liquid that a child may take, GSK should make that argument."

The sponsor requested a partial waiver for conducting clinical studies in pediatric patients below 13 years of age with the proposed XR lamotrigine and made the following arguments.

"Extended release tablet formulations not ideal for use in children given the dosing considerations necessary for lamotrigine

The dosing complexity for pediatric patients taking lamotrigine is however highly problematic for any formulation that cannot be administered in a single administration as can the CD tablet. Since the extended-release tablets must be ingested whole and is not formulated to be chewed or dispersed in liquid, many patients would need to ingest multiple tablets. The primary advantage of the lamotrigine XR extended-release formulation is the simplification of treatment with once a-day dosing which for most adult patients can be accomplished with the administration of single tablet. While once–a-day dosing with lamotrigine XR extended-release tablets may be achieved in pediatric patients, this would, in many cases, require the administration of multiple tablets with each dose. While it is expected that once-a-day dosing may improve compliance over that seen with more frequent daily dosing, this seems less likely to be the case if the once-a-

day dosing complicates administration by requiring the pediatric patient to take multiple whole tablets.

From a formulation perspective, to achieve the large potential dose range required with levels as high as 285mg at 19kg (i.e. age 5) and up to 570mg at 38kg (i.e. age 12) while maintaining good compliance on the dose levels administered, a tablet is the most appropriate of the standard controlled release formulation delivery technologies. For controlled release solutions and suspensions the requirement for such high dose levels would not be considered applicable. Other formulations such as sprinkles at these dose levels would be problematic to ensure dose compliance, requiring emptying of multiple capsules without loss of contents and ensuring the full, large quantity of sprinkles, are swallowed with food whilst ensuring no break up of the sprinkle particles in the oral cavity by chewing. Whereas the chewable dispersible tablet provides both flexibility to allow swallowing whole, chewed or administered as a dispersion of multiple tablets, according to personal patient preference while providing good control on the dose administered on a mg/kg basis.

The currently available Lamictal CD tablets achieve the optimal flexibility of dosing needed to address the complexity of dosing with lamotrigine in the pediatric age range. The lamotrigine XL extended-release formulation does not provide a benefit to the pediatric population over and above that of the CD tablet.

Thus, a partial waiver for conducting clinical studies in pediatric patients below 13 years of age with the proposed extended-release formulation is requested."

The Clinical Pharmacology review noted :

"Although there are few subjects between the age range of 13-18 years, additional PK study is not necessary in this age group because (i) concentrations (and doses) were similar to the adults and there were at least 4-6 samples per subject; (ii) effectiveness of lamotrigine IR in the age range 12-18 years has been established and dosing in partial seizures for the IR formulation is same for ages 12 and older; (iii) relative bioavailability to the IR formulation in patients is known (overall 90% relative BA), hence overall the exposures are not expected to be very different."

Reviewer Comment

- I do not find the sponsor's argument for requesting a pediatric waiver for patients < 13 years old to be very convincing or compelling. The present NDA does not support the efficacy and safety of XR lamotrigine in any pediatric patients. If XR lamotrigine is approved for adults (≥ 16 years), I believe that the sponsor should make a phase 4 commitment to develop and study XR lamotrigine for pediatric patients. The main question is what should be the lower pediatric age limit for this development of the XR formulation?

8.5 Advisory Committee Meeting

- Not applicable

8.6 Literature Review

The sponsor did not present a literature review.

8.7 Postmarketing Risk Management Plan

8.8 Other Relevant Materials

- Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

Sponsor Conclusions :

Sponsor Efficacy Conclusions

• The median percent reduction from Baseline in all partial seizure frequency during ,the entire Treatment Phase was greater in the LTG XR group (46.1%) than in the placebo group (24.2%) (p=0.0004) for the ITT Population.

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

• The percentage of subjects who showed a ≥50% reduction in all partial seizure frequency over the entire Treatment Phase was greater in LTG XR group (42.2%) compared with the placebo group (24.2%, p=0.0037) for the ITT Population.

• Time (in weeks) to ≥50% reduction in seizure frequency for the entire Treatment Phase was shorter for the LTG XR group compared with the placebo group (p=0.0007) for the ITT Population. Statistical significance was seen as early as Day 18 (p=0.0448).

• There were differences in the ITT Population between the two treatment groups in the frequency distribution of the investigator's global assessment of subjects' overall clinical status in favor of LTG XR (p=0.0012).

• No effect of race, age, country, AED group, gender or historical baseline use on percent change from Baseline in any seizure type during the entire Treatment Phase was observed.

Sponsor Safety Conclusions

•Lamotrigine IR has a well established safety profile. The safety profile for lamotrigine XR is consistent with current labeling and previous experience with lamotrigine IR. The results of the clinical program and pivotal clinical study LAM100034 demonstrate that lamotrigine XR has an acceptable tolerability profile as adjunctive therapy in subjects ≥13 years of age with partial seizures.

• The safety profile of lamotrigine XR in healthy volunteers is generally consistent with the well-characterized safety profile in lamotrigine IR.

• The most common drug-related AEs in healthy volunteers receiving lamotrigine XR were headache, nausea, rash, dizziness, agitation, ocular hyperemia and vision blurred.

• Adverse events were generally of mild to moderate intensity.

• There is no evidence of a dose-related AE effect associated with lamotrigine XR treatment.

• No SAEs were seen in any of the clinical pharmacology studies.

• Lamotrigine XR is associated with low rates of withdrawal due to AEs. The most common AE leading to withdrawal in healthy subjects receiving lamotrigine XR is rash.

• There is no evidence of an adverse effect of lamotrigine XR on ECG, laboratory results, vital signs or physical examination findings.

• Lamotrigine XR is generally safe and well-tolerated in healthy volunteers.
• The AE profile for lamotrigine XR is consistent with previous experience with lamotrigine IR. The type of AEs in pivotal clinical study LAM100034 and in studies LAM100034 and LAM100036 combined were similar to those reported in the current labeling for lamotrigine IR.

• The most common AEs in subjects receiving lamotrigine XR in studies LAM100034 and LAM100036 combined were headache (13%), dizziness (13%), nausea (7%) and vomiting (5%). Dizziness (10%) was the most frequently reported drug-related AE in subjects receiving lamotrigine XR.

• Three deaths occurred during the study in LAM100034. One subject randomized to the lamotrigine XR group died prior to receiving study medication in LAM100034. Two deaths in

subjects receiving lamotrigine XR occurred during the Open-label Continuation Phase of study LAM100034. None of these events were judged to be related to study medication by the investigator.

• In the LAM100034 and LAM100036 combined database, a total of 13 (4%) subjects experienced non-fatal SAEs. Nystagmus was the only SAE reported in more than one subject.

• In studies LAM100034 and LAM100036 combined, the overall incidence of rash on lamotrigine XR in unblinded subjects was 4% (13 subjects). Rash was considered to be reasonably attributable to study drug for 6 (2%) subjects receiving lamotrigine XR and two (<1%) subjects receiving lamotrigine XR were discontinued due to rash. There were no cases of serious rash as defined in the LAMICTAL product label during any study in the lamotrigine XR program (i.e., associated with hospitalization and the discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis). There were no cases of Stevens-Johnson Syndrome or toxic epidermal necrolysis.

• There were no clinically meaningful treatment-emergent changes in clinical laboratory evaluations attributed to lamotrigine XR in studies LAM100034 and LAM100036 combined.

• Vitals sign changes were consistent with the age of the population and there were very few clinically significant ECG abnormalities changes from screen in study LAM100034.

• There was no observed difference between placebo and lamotrigine XR with respect to weight (mean change from Baseline: -0.06kg; 90% CI: -0.775, 0.664) in study LAM100034.

• In study LEP103944, the safety and tolerability of lamotrigine XR once daily compared to lamotrigine IR twice daily, in subjects with epilepsy, was comparable.

• The only AEs reported by ≥5% of subjects during any treatment phase in the LEP103944 CSR were headache and nasopharyngitis. The only study drug related AE reported by ≥5% of subjects during any treatment phase was headache.

• No deaths occurred during this study. One SAE occurred during the course of this study; during the Extended-release Phase, one (3%) subject experienced increased seizure activity (coded as convulsion) which was considered by the investigator as not related to study drug.

• Three subjects experienced AEs that led to discontinuation; none of these events were considered by the investigator to be related to study drug.

• The information included in the lamotrigine Global Data Sheet and the US prescribing information reflects the post-marketing experience with lamotrigine to date.

Reviewer Conclusions

Efficacy Conclusion

- **I am unable to conclude that XR lamotrigine is effective as adjunctive treatment of partial epilepsy in adults based upon my concerns outlined about the lack of efficacy with U.S. data and questions about the quality of the foreign data that drive the demonstration of efficacy.**

Safety Conclusions

- There is no clear evidence that the safety profile for XR lamotrigine treatment is different than that recognized for approved IR lamotrigine treatment.

- There may be some relatively minor differences in the overall safety profile (relative to types of TEAEs and the period of greatest risk for these TEAEs) of XR lamotrigine treatment vs that for IR lamotrigine treatment (see section 7.1.4 Other Search Strategies that contains this information and suggestive analyses). However, it is not clear whether the relatively minor differences may be related to the analyses conducted in this NDA vs analyses previously conducted for IR lamotrigine.

- I have concerns and suspicions that lamotrigine may produce notable changes in vital signs that may warrant description in the label. However, analyses of vital signs for studies LAM100034 and SCA104648 are not appropriate and additional analyses (especially for outliers) should be requested. My concerns about vital sign analyses are outlined in sections 7.1.8 and 7.1.12.

9.2 Recommendation on Regulatory Action

- I recommend an approvable action because I cannot clearly conclude that XR lamotrigine is effective for adjunctive treatment of partial epilepsy in adults. The sponsor needs to address adequately the reason that XR does not appear to be effective in U.S. patients (that comprised nearly 40 % of all randomized patients) and why there should not be an Agency concern that the demonstration of efficacy is driven by solely foreign data in the sole pivotal study designed to demonstrate efficacy of XR lamotrigine.

    - If the sponsor cannot adequately explain the lack of efficacy in U.S. patents and address and satisfy Agency concerns, the sponsor should conduct another pivotal efficacy study either solely in the U.S. and/or in other locations (e.g. Canada, western European countries) in which the Agency generally has confidence in the quality of clinical data collection.

    - The results of the pending DSI inspections of 2 Korean sites have not yet been received (as of 9/14/07). However, the recently received (9/14/07) communication

(9/10/07 cover letter) from the sponsor describing several, various errors (including efficacy seizure rate data) in transcribing source data to CRFs raises serious questions about the quality of data not only at these 2 foreign sites but also at potentially many other foreign sites.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

- Not applicable at this time

9.3.2 Required Phase 4 Commitments

Reviewer Comment

- If XR lamotrigine is approved for adults (≥ 16 years), I believe that the sponsor should make a phase 4 commitment to develop and study XR lamotrigine for pediatric patients. The present NDA does not support the efficacy and safety of XR lamotrigine in any pediatric patients. I do not find the sponsor's argument for requesting a pediatric waiver for patients < 13 years old to be compelling. The main question is what should be the lower pediatric age limit for this development of the XR formulation?

9.3.3 Other Phase 4 Requests

- Not applicable at this time

9.4 Labeling Review

Reviewer Comment

- A separate draft labeling review by this reviewer is being prepared showing the tracked changes of the sponsor's proposed draft labeling.

9.5 Comments to Applicant

- If an approvable letter is the result of our action, appropriate comments/recommendations resulting from a divisional consensus will be sent to the sponsor.

10 APPENDICES

- Not applicable

10.1 Review of Individual Study Reports

- Not applicable

10.2 Line-by-Line Labeling Review

- A labeling review recommended by this reviewer will be generated and provided to the Clinical Team Leader for developing into a DNP recommended label for consideration by the sponsor.

REFERENCES

- Not applicable

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/s/

Leonard Kapcala
10/4/2007 02:01:23 PM
MEDICAL OFFICER

John, Here is my clinical review that you have seen previously. Please sign and let me know if any questions. Thanx. Len

John Feeney
10/26/2007 10:33:57 PM
MEDICAL OFFICER
Noted

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22115
Brand Name	Lamictal XR
Generic Name	lamotrigine
Sponsor	GlaxoSmithKline
Indication	Treatment of epilepsy (b) (4)
Dosage Form	Extended-Release Tablets
Therapeutic Dose	Up to 500 mg/day in divided doses as monotherapy
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not defined
Application Submission Date	22 March 2007
Review Classification	TQT Study Report
Date Consult Received	04 June 2007
Date Consult Due	20 August 2007
Clinical Division	DNP / HFD 120
PDUFA Date	22 September 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Study SCA104648 was a 'thorough QT' study sponsored by GlaxoSmithKline and submitted to support NDA 22-115, an application to market an extended release formulation of a currently marketed product, LAMICTAL® (lamotrigine). The study attempted to assess the effect of administering immediate release lamotrigine on the QTc in healthy subjects. The study had multiple major deficiencies in design and conduct (see comments below). Nonetheless, the QT-IRT is persuaded by the sponsor's data that the highest plasma concentrations of lamotrigine likely be to achieved after administration of the highest recommended dose of immediate release or extended release LAMICTAL® will not prolong the QT interval. In fact, administration appears likely to shorten the QT interval modestly.

We do not accept the sponsor's assertion that study SCA104648 was a negative thorough QT study because the primary analysis was flawed for the reasons we review in our comments below. However, the results of the concentration-QT analysis show a trend to shorter QTc with increasing doses. In addition, an FDA conducted examination of the post-marketing database does not suggest that lamotrigine is associated with increased death rate, torsade de pointes or QT prolongation. Therefore the QT-IRT thinks it unlikely that lamotigine administration is associated with QT interval prolongation or

serious ventricular arrhythmias. However, we acknowledge that a different observer might reasonably come to a different conclusion given the flaws in study SCA104648.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

All of the following deficiencies tend to lower confidence in the reliability of the primary analysis.

- The exposures achieved in study SCA104648 failed to cover the highest exposures that can be reasonably expected to occur after administration of therapeutic doses of Lamictal and Lamictal XR. Co-administration of doses up to 250 mg with valproic acid are described in the PI. Taking PK interactions with valproic acid into account, this dose is equivalent to a monotherapy daily dose of 500 mg lamotrigine. The highest dose studied in this study was 200 mg bid.

  However other studies suggest that doses as high as 500 mg are not tolerable by healthy volunteers. Conducting a TQT study in patients with partial seizures might be challenging, as most of these patients would be on combination therapies confounding interpretation of the results.

- The sponsor conducted a two stage study with moxifloxacin administered to subjects only during the first stage. This design is problematic for the following reasons: 1) The effects on the QTc can be detected more sensitively since there were more subjects (and so more data) in the first stage; 2) The effects on the QTc can be detected more sensitively in the first stage because it was a crossover study so variance was reduced (since each subject served as their own control) compared with the parallel study conducted in the second stage; and 3) The period effect (stage 1 and stage 2) may be confounded by the treatment effect Therefore, using the first stage, which was conducted in a different way from the second stage, to claim assay sensitivity in the second stage is not valid.

2 BACKGROUND

Lamotrigine inhibits voltage-sensitive sodium channels by stabilizing them in the inactivated state. It is believed that lamotrigine at therapeutic concentrations selectively and significantly reduces rapid repetitive firing of sodium-dependent action potentials during epileptiform activity, but does not disturb normal neuronal transmission.

The LAMICTAL® brand of lamotrigine is currently marketed as an immediate-release compressed or chewable/dispersible tablet. The pending NDA 22-115 is for a new extended release formulation of lamotrigine and the TQT was submitted to this NDA in the 120 Day Safety Update report.

2.1 DRUG CLASS

Phenyltriazine anticonvulsant

2.2 MARKET APPROVAL STATUS

LAMICTAL® was first approved by the USFDA in December 1994 (NDA 20-241) for adjunctive treatment of partial seizures in adults. Its current approved indications include (from the current label):

- Adjunctive Use: LAMICTAL® is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adult and pediatric patients (≥ 2 years of age).
- Monotherapy Use: LAMICTAL® is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single anti-epileptic drug.
- Bipolar Disorder: LAMICTAL is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

The recommended dose is to titrate over several weeks to 300 – 500 mg in 2 divided doses. The label mentions that doses up to 700 mg/day may be needed if drugs that induce glucuronidation are being co-administered.

2.3 PRECLINICAL INFORMATION

The current IB states "In a(n) in vitro assay using HEK293 cells stably expressing hERG channels, lamotrigine was found to inhibit hERG channel tail current in a concentration-dependent manner (7.1677 to 215.031 µM), with nominal IC_{25} and IC_{50} values of 104 and 323 µM respectively."

"Lamotrigine has been studied in the rat dog and monkey following oral and intravenous administration and in vitro systems (guinea pig myocytes, dog Purkinje fibres…these studies were conducted in the mid 1980s to mid 1990s using testing methodologies that were standard for this time period. Lamotrigine did not produce evidence of an effect on cardiac repolarisation or prolongation of the QT interval in these test systems."

2.4 PREVIOUS CLINICAL EXPERIENCE

2.4.1 Sponsor report

The sponsor states "After more than 10 years of marketing experience with cumulative exposure to lamotrigine estimated 5.2 million patient-years, eleven case reports of QT interval prolongation have been reported to GSK. No cases of torsades de pointes were received. Of note, over 17,000 lamotrigine spontaneously reported and serious clinical trial adverse events have been reported to date. Medical review of these eleven reports of QT interval prolongation following lamotrigine treatment did not indicate a safety signal with respect to either QT interval prolongation or associated cardiac arrhythmias. It was evident that the reported events of QT interval prolongation could have been associated with other factors, such as concomitant medications, concurrent medical conditions, or as a result of an overdose of lamotrigine in combination with other agents, rather than use of lamotrigine in recommended therapeutic doses.

"There have been no AEs of concern (sudden death, torsades de pointes, ventricular tachycardia, QTc prolongation, cardiac arrest, palpitations, tachycardia, syncope) reported in any of the healthy volunteer studies conducted to date.

"ECG data from US-controlled trials (in epilepsy) demonstrated no tendency for lamotrigine to significantly affect heart rate, QRS duration or QT interval."

2.4.2 FDA assessment of post-marketing experience

Dr. Ana Szarfman performed a safety data mining analysis of the FDA Adverse Event Reporting System (AERS) database for lamotrigine using the Multi-item Gamma Poisson Shrinker (MGPS) data mining method. The chief results are as follows:

- Lamotrigine's data mining signal scores demonstrated signals of Stevens-Johnson syndrome, toxic epidermal necrolysis and other serious skin events, and sudden death, but no major cardiac arrhythmias.

Reviewer's comment: The PI for LAMICTAL® has a black box warning for serious rashes so the method used by Dr. Szarfman appears sensitive enough to accurately identify some serious adverse events associated with lamotrigine administration.

- Lamotrigine's data mining signal scores for "sudden cardiac death" and "sudden death," are similar to those of the comparator drugs carbamazepine, gabapentin, phenytoin, and valproic acid.

Table 1: Data Mining Signal Scores for the Preferred Terms "Sudden Cardiac Death" and "Sudden Death" with Lamotrigine and Comparator Drugs

Event	Generic name	N	EB05	EBGM	EB95
Sudden cardiac death	Lamotrigine	3	0.365	0.932	2.048
	Gabapentin	2	0.234	0.712	1.768
	Carbamazepine	1	0.132	0.556	1.704
	Phenytoin	1	0.129	0.543	1.663
Sudden death	Lamotrigine	47	1.958	2.5	3.153
	Gabapentin	37	1.49	1.962	2.546
	Carbamazepine	39	1.374	1.797	2.317
	Valproic Acid	44	1.327	1.708	2.171
	Phenytoin	9	0.224	0.391	0.646

*** Lamotrigine values are in green. In red, non-overlapping higher (EB05, EB95) interval for the comparator; in blue, overlapping confidence interval; in black, non-overlapping and lower (EB05, EB95) than Lamotrigine.**

Reviewer's comment: Epileptics have an increased incidence of sudden death, termed sudden unexplained death in epilepsy. Lamotrigine does not appear to detectably increase the sudden death rate compared with other anti-epileptic drugs

- Very few cases of sudden death were associated with the concomitant use of lamotrigine and valproic acid, a drug known to increase lamotrigine levels. In contrast data mining shows increased signal scores of toxic epidermal necrolysis with concomitant administration of lamotrigine and valproic acid.

Reviewer's comment: This finding suggests no dose dependent increase in reports coded as sudden death or sudden cardiac death after co-administration of lamotrigine with valproic acid.

- Lamotrigine's data mining signal scores for Torsade de pointes and prolonged QT are similar to those of the comparator drugs carbamazepine, gabapentin, phenytoin, and valproic acid.

Table 2: Data Mining Signal Scores for the Preferred Terms "Torsade De Pointes," "Electrocardiogram QT Corrected Interval Prolonged," and "Electrocardiogram QT Prolonged" with Lamotrigine and Comparator Drugs

Event	Generic name	N	EB05	EBGM	EB95
Torsade de pointes	Valproic Acid	14	0.587	0.92	1.387
	Gabapentin	6	0.268	0.529	0.961
	Carbamazepine	5	0.232	0.487	0.928
	Lamotrigine	4	0.186	0.424	0.859
	Phenytoin	4	0.15	0.343	0.693
Electrocardiogram QT corrected interval prolonged	Gabapentin	10	0.732	1.245	2.008
	Valproic Acid	10	0.677	1.15	1.855
	Phenytoin	3	0.213	0.543	1.193
	Lamotrigine	2	0.074	0.226	0.562
	Carbamazepine	1	0.051	0.215	0.66
Electrocardiogram QT prolonged	Carbamazepine	21	0.619	0.893	1.255
	Valproic Acid	27	0.638	0.881	1.192
	Lamotrigine	14	0.446	0.698	1.053
	Phenytoin	11	0.292	0.485	0.767
	Gabapentin	9	0.273	0.478	0.788

*** Lamotrigine values are in green. In red, non-overlapping higher (EB05, EB95) interval for the comparator; in blue, overlapping confidence interval; in black, non-overlapping and lower (EB05, EB95) than Lamotrigine.**

- Only 4 cases of Torsade de pointes were identified. All had confounding factors.

2.4.3 Current Product Insert

LAMICTAL® has a black box warning for serious rashes requiring hospitalization including the Stevens-Johnson syndrome. The recommended dose for epilepsy is up to 500 mg/day in two divided doses after slow up-titration to minimize the incidence of severe rash.

2.5 CLINICAL PHARMACOLOGY

Table 3 summarizes the key features of lamotrigine's clinical pharmacology.

Table 3: Highlights of Clinical Pharmacology (1 of 6 pages)

Therapeutic dose	**Immediate-release lamotrigine (currently approved maintenance doses)** • Monotherapy: 500mg/day in two divided doses • For patients taking valproate: 100-400mg/day in 1 or 2 doses (100-200/day with valproate alone) • For patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate: 225-375mg/day in 2 divided doses • For patients taking carbamazepine, phenytoin, phenobarbital, primidone, and NOT taking valproate: 300-500/day in 2 divided doses (b) (4)
Maximum tolerated dose	The maximum dose used in clinical trials with Lamictal occurred in open-label continuation studies in which titration to clinical effect was permitted. In these studies 34 patients had LTG concentrations greater than 16 ug/ml approximating a monotherapy dose of Lamictal of at least 1,000 mg qd. There are clear dose-related CNS side effects of Lamictal, primarily dizziness, ataxia and double-vision, that limit the use of higher doses. This has best most recently been clearly elucidated by Hirsch et al who reported the relationship between LTG concentration and adverse events in 811 patients from the Columbia Comprehensive Epilepsy Center. In this study increasing CNS toxicity requiring a dose adjustment of LTG was seen with higher concentrations of LTG. Concentrations of LTG < 5 ug/ml, 5-10 ug.ml, 10-15 ug/ml, 15-20 ug.ml and > 20 ug/ml were associated with Aes requiring LTG dose reduction in 7%, 14%, 24% 34% and 59% of patients respectively. Concentrations of 20 ug/ml would be associated with a monotherapy dose of Lamictal of approximately 1250 mg qd. Thus the maximum tolerated dose varies widely across patients but is consistently limited by readily recognized, nonserious, CNS signs of toxicity.

Highlights of Clinical Pharmacology (2 of 6 pages)

Principal adverse events	**Volunteers** Dizziness and ataxia as well as nausea and headache. Ataxia, blurred vision, diplopia, dizziness, nausea and vomiting are dose-related. **Epilepsy Patients**: Same as above Treatment-limiting adverse event is serious rash requiring hospitalization. There are suggestions that high initial doses and fast titration may increase the risk of serious rash, particularly with concomitant valproate.	
Maximum dose tested	Single Dose	450mg (volunteers-monotherapy) 480mg (patients on concomitant AEDs)
	Multiple Dose	400mg qd X 10 days (volunteers-monotherapy) 350mg bid X 7 days (patients on concomitant AEDs)
Exposures Achieved at Maximum Tested Dose	Single Dose	450mg (volunteers-monotherapy) Cmax 6.5mcg/mL (6.6%) AUC 304.7 h.mcg/mL (19.1%) 480mg (patients on concomitant AEDs) Cmax 5.9mcg/mL (32.1%) AUC 171.5 h.mcg/mL (66.5%)
	Multiple Dose	400mg qd X10 days (volunteers-monotherapy) Cmax 8.6mcg/mL (21.0%) AUC 131.7 h.mcg/mL (17.5%) 350mg bid X7 days (patients on concomitant AEDs) Cmax 6.4mcg/mL (48.4%) AUC 57.7 h.mcg/mL (47.1%)
Range of linear PK	50-400 mg (single dose in volunteers) 50-350 mg twice daily (patients maintained on other AEDs)	
Accumulation at steady state	None	
Metabolites	2-N-glucuronide (76% of an administered dose); inactive 5-N-glucuronide (10%); inactive 2-N-methyl metabolite (0.14%); no anticonvulsant activity, decreased cardiac conduction in dogs Other unidentified minor metabolites (4%)	

Highlights of Clinical Pharmacology (3 of 6 pages)

Absorption	Absolute/Relative Bioavailability	98% (%CV ND)
	Tmax	• **Mean (range) for parent** 1.3-4.7 hours depending on concomitant AED therapy • **Mean (range) for metabolites** Not determined
Distribution	Vd/F or Vd	Vd/F 1.2 L/kg
	% bound	53- 56%
Elimination	Route	Primary route is metabolism via glucuronic acid conjugation Major metabolite is hydrolysable 2-N-glucuronide conjugate 70% of an oral dose excreted as 2-N-glucuronide in urine. <10% of an oral dose excreted as unchanged lamotrigine in urine
	Terminal t½	• Mean for parent **NOTE:** **Single dose t½ is longer than multiple dose t½ as lamotrigine induces its own metabolism upon repeat dosing.** **Half-life of lamotrigine is affected by concomitant AEDs that are inducers or inhibitors of glucuronidation. Values below are mean (range)** Volunteers monotherapy : 32.8h (14-103) single dose 25.4h (11.6-61.6) multiple dose Volunteers concomitant valproate (inhibitor): 48.3h (31.5-88.6) single dose 70.3h (41.9-113.5) multiple dose Epilepsy patients concomitant valproate (inhibitor): 58.8h (30.5-88.8) single dose Epilepsy patients concomitant carbamazepine, phenytoin, phenobarbital, or primidone (inducers):

Highlights of Clinical Pharmacology (4 of 6 pages)

		14.4h (6.4-30.4) single dose 12.6h (7.5-23.1) multiple dose Epilepsy patients concomitant carbamazepine, phenytoin, phenobarbital, or primidone **plus** valproate: 27.2h (11.2-51.6) single dose • Mean (%CV) for metabolites: Not determined
	CL/F or CL	**NOTE: clearance of lamotrigine is affected by concomitant AEDs that are inducers or inhibitors of glucuronidation. Values below are mean (range).** Monotherapy (volunteers): 0.44mL/min/kg (0.12-1.10) single dose 0.58mL/min/kg (0.24-1.15) multiple dose Concomitant valproate (volunteers): 0.30mL/min/kg (0.14-0.42) single dose 0.18mL/min/kg (0.12-0.33) multiple dose Concomitant valproate (epilepsy patients): 0.28mL/min/kg (0.16-0.40) single dose Concomitant carbamazepine, phenytoin, phenobarbital, or primidone **plus** valproate (epilepsy patients): 0.53mL/min/kg (0.27-1.04) single dose Concomitant carbamazepine, phenytoin, phenobarbital, or primidone (epilepsy patients): 1.10mL/min/kg (0.51-2.22) single dose 1.21mL/min/kg (0.66-1.82) multiple dose
Intrinsic Factors	Age	**Elderly:** Cmax, AUC similar (comparison vs other volunteer studies in younger adult patients) **Pediatrics:** Cmax, AUC not evaluated. Population pharmacokinetic analyses involving patients aged 2 to

Highlights of Clinical Pharmacology (5 of 6 pages)

		18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg
	Sex	Changes in Cmax, AUC not evaluated In a population PK analysis there was a small (7%) but statistically significant difference in CL/F between males and females which is not considered to be clinically relevant.
	Race	Changes in Cmax, AUC not evaluated A population PK analysis conducted for patients receiving lamotrigine monotherapy showed that oral clearance in Asians was 30% lower than for Caucasians. In patients on adjunctive therapy, a population PK analysis showed that oral clearance in non-Caucasians was 25% lower than in Caucasians.
	Hepatic & Renal Impairment	**Hepatic Impairment:** Moderate cirrhosis: No change in Cmax or AUC Severe cirrhosis without ascites: No change in Cmax; 60% increase in AUC Severe cirrhosis with ascites: No change in Cmax, 260% increase in AUC **Renal Impairment:** Renal failure patients (mean creatinine clearance 13mL/min): No change in Cmax; 82% increase in AUC
Extrinsic Factors	Drug interactions	**Oral contraceptives (ethinylestradiol/levonorgestrel):** 39% decrease in Cmax, 52% decrease in AUC **Olanzapine:** 20% decrease in Cmax, 24% decrease in AUC **Rifampin:** Cmax not determined, AUC decreased by 40% **Carbamazepine, Phenobarbital, phenytoin, primidone:** Cmax, AUC not determined. Cl/F increased by 100%, steady state concentrations decreased by 40%

Highlights of Clinical Pharmacology (6 of 6 pages)

		Valproate: Cmax, AUC not determined, steady state concentrations increased by more than 2-fold **NO EFFECT ON LAMOTRIGINE PHARMACOKINETICS:** Bupropion, felbamate, gabapentin, levetiracetam, pregabalin, topiramate, zonisamide
	Food Effects	No effect on Cmax, AUC; mean Tmax increased from 2 to 3.4 hours (immediate-release). Meal:13.1% protein, 47.3% fat, 39.6% carbohydrate
Expected High Clinical Exposure Scenario	Worst case scenario would be a patient receiving a monotherapy dose of Lamictal 1000mg/day plus an estrogen-containing oral contraceptive (maximum per current approved labeling). If the oral contraceptive is then discontinued and valproate is added while leaving the Lamictal dose at 1000mg/day, the expected increase in Cmax and AUC would approximate those of a Lamictal dose of 2000mg/day, which is 4 times the currently recommended monotherapy dose of 500mg/day.	

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The sponsor submitted a 'thorough QT' study in a 120 Day Safety Update report to NDA 22-115.

3.2 'THOROUGH QT' STUDY

3.2.1 Title

A study to evaluate the effect of repeat oral doses of lamotrigine on cardiac conduction as assessed by 12-Lead ECG as compared to placebo and single oral doses of moxifloxacin.

3.2.2 Protocol Number

SCA104648

3.2.3 Objectives

3.2.3.1 Primary

Estimate the effect of steady state oral dosing of lamotrigine IR and single dose moxifloxacin on the QTcF relative to placebo.

3.2.3.2 Secondary

- Estimate the effect of steady state oral dosing of lamotrigine and single dose moxifloxacin on QTcB, PR and heart rate relative to placebo.
- Characterize the pharmacokinetics of steady state lamotrigine and single dose moxifloxacin and to investigate the concentration-QTc effect relationship for lamotrigine

3.2.4 Design

3.2.4.1 Description

The study was conducted in two parts. The first part was a randomized, open label, 2 period, crossover, single dose study of administering moxifloxacin to establish assay sensitivity. Subjects were randomized to one of two treatment groups, Treatment Group 1 or Treatment Group 2. An oral dose of either moxifloxacin 400 mg or "placebo" (which did not look like moxifloxacin) was administered randomly in a "treatment session" 1 and the other was administered in "treatment session" 2 with a 7 day washout period between each session. Electrocardiograms were recorded and pharmacokinetic samples were taken for 24 hours post-dose during each session.

The second part was a randomized, double-blind, parallel group study to evaluate the QT effect of lamotrigine and began after another 7 day washout period. Subjects assigned to Treatment Group 1 received increasing doses of LAMICTAL® over 77 days, while those assigned to Treatment Group 2 received placebo. To maintain the blind, subjects in each group received the same number of tablets. Electrocardiograms were recorded and pharmacokinetic samples were taken for 12 hours post-dose on Day 42 (session 3) when the dose of LAMICTAL® had been titrated to 50 mg bid, Day 63 (session 4) at a dose of 150 mg bid and Day 77 (session 5) at a dose of 200 mg bid.

3.2.4.2 Sponsor's Justification for Design

The slow up-titration required to achieve steady state to minimize the occurrence of rash necessitated a long duration of dosing and this precluded a crossover design.

3.2.4.3 Controls

The Sponsor used both negative (placebo) and positive (moxifloxacin) controls.

3.2.4.4 Blinding

Moxifloxacin was administered open label.

3.2.5 Dosing Regimens

3.2.5.1 Treatment Arms

Subjects were randomized to one of the following sequences with a 1:1:1:1 allocation ratio (sequences 1 and 2 were Treatment Group 1 in which LAMICTAL® was administered while 3 and 4 were Treatment Group 2 in which placebo was administered):

- Sequence 1: ABCDEFGHIJKL
- Sequence 2: BACDEFGHIJKL
- Sequence 3: ABMNOPQRSTUV
- Sequence 4: BAMNOPQRSTUV

Where the treatments were as follows:

A. Moxifloxacin 400 mg
B. Moxifloxacin "placebo"

C. LAMICTAL® 25 mg qd day 1-14
D. LAMICTAL® 25 mg bid day 15-28
E. LAMICTAL® 50 mg bid day 29-42
F. LAMICTAL® 100 mg bid day 43-49
G. LAMICTAL® 150 mg bid day 50-62
H. LAMICTAL® 200 mg bid day 64-77
I. LAMICTAL® 150 mg bid day 78-79
J. LAMICTAL® 100 mg bid day 80-81
K. LAMICTAL® 50 mg bid day 82-83
L. LAMICTAL® 25 mg bid day 84-85
M. – V. Placebo

3.2.5.2 Sponsor's Justification for Doses

In study LAM10016 the plan was to titrate LAMICTAL® to a dose of 500 mg/day in healthy female subjects to assess the effects of the combined oral contraceptive pill on lamotrigine pharmacokinetics. However CNS AEs were seen in 5/11 subjects at 400 mg/day and the dose was reduced to 300 mg/day. The sponsor concluded that normal volunteers would not tolerate doses in excess of 400 mg/day.

Reviewer's comment: Due to lack of tolerability, study SCA104648 *did not include a supratherapeutic dose or even the current highest approved LAMICTAL® dose of 500 mg/day for monotherapy in epilepsy. Hence the exposures achieved in this study did not cover the exposures expected after administration in clinical practice.*

3.2.5.3 Instructions with regard to meals

For each ECG assessment day, including baseline (Day -1) assessments, subjects were to fast from all food and drink (except water) for at least 10 h prior to administration of study medication and continue fasting for at least 4 h following dosing. Water was permitted starting at 2 hr following dosing.

3.2.5.4 Study Assessments

Table 4: Highlights of Schedule of Interventions

Procedure	Sessions 1 and 2 (Days -1 to 1)	Session 3 (Days -1 – 42)	Session 4 (Days 43 – 63)	Session 5 (Days 64 – 77)	Down-titration (Days 78 – 85)
Serial 12-lead electrocardiography[b]	Day 1: Pre-dose (-1 h, -30 min, -5 min), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h post-dose.	Day 1: Pre-dose (-1 h, -30 min, -5 min), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-dose.. Day 42: Pre-dose (-1 h, -30 min, -5 min), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-dose.	Day 63: Pre-dose (-1 h, -30 min, -5 min), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-dose.	Day 77: Pre-dose (-1 h, -30 min, -5 min), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-dose.	Day 85: pre-dose.
Vital signs [supine/standing]	Day 1: Pre-dose, 2, 8, 22 – 24 h post-dose.	Day 42: Pre-dose, 2, 8, 22 – 24 h post-dose.	Day 63: Pre-dose, 2, 8, 22 – 24 h post-dose.	Day 77: Pre-dose, 2, 8, 22 – 24 h post-dose.	Day 85: pre-dose.
Clinical laboratory	Day -1.	Day 42: pre-dose.	Day 63: pre-dose.	Day 77: pre-dose.	Day 85: pre-dose.
Pharmacokinetic sampling	Moxifloxacin/placebo Day 1: pre-dose, 0.25, 0.50, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 12, 24 h post-dose.	Lamotrigine/placebo Day 42: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h post-dose.	Lamotrigine/placebo Day 63: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h post-dose.	Lamotrigine/placebo Day 77: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h post-dose.	Not applicable
Pre-dose pharmacokinetics	Not applicable.	Days 40, 41: pre-morning-dose.	Days 61, 62: pre-morning-dose.	Days 75, 76: pre-morning-dose.	Not applicable.
Pharmacogenetics (if consented)	Session 1 Day 1 pre-dose.	Not applicable.	Not applicable.	Not applicable.	Not applicable.

a. Out-patient clinic visits: subjects attended the clinic for dosing with breakfast.
b. Twelve-lead ECGs were to be obtained prior to any other assessment scheduled, following immediately by vital signs and pharmacokinetic blood draws. Electrocardiography measurements were taken in triplicate approximately 1 minute apart. Pre-dose ECG assessments were taken immediately prior to the dosing of study medication.

3.2.5.5 Sponsor's justification for sampling schedule

No justification provided.

3.2.5.6 Baseline

The steps involved in the derivation of the mean value and change from baseline value in ECG parameters at each time point were as follows:

- For session 1 the baseline for ECG values was the average of the replicate ECG observations on Session 1 Day 1: Pre-dose (-1 h, -30 minutes, -5 minutes) - average of the three means.
- For session 2 the baseline for ECG values was the average of the replicate ECG observations on Session 2 Day 1: Pre-dose (-1 h, -30 minutes, -5 minutes) - average of the three means.
- For sessions 3 to 5 the baseline for ECG values was the average of the replicate ECG observations on Session 3 Day 1: Pre-dose (-1 h, -30 minutes, -5 minutes) -average of the three means

Reviewer's comment: During a parallel study time-match baseline ECGs should be acquired to account for diurnal variability in the QTc. In study SCA104648 the QTc baseline was an average of the replicate ECG observations on Day 1 at three pre-dose time points, -1 h, -30 minutes, -5 minutes.

3.2.6 ECG Collection

12-Lead Holter monitoring was used to obtain digital ECGs. Subjects remained in the supine position for the 30- minute pre-dose period on ECG profile days and on bed-rest either semi-supine or supine until 4 h after dosing (excluding the blood pressure recordings when subjects were required to sit and then stand). In addition, after the 4 h

post-dose subjects were to rest in the supine position for 15 minutes before each scheduled ECG recording time point.

All ECGs were digitally acquired and transmitted to a specified core lab for digital caliper analysis. Triplicate ECGs were taken during each assessment, 1 minute apart, at each time point. Conduction intervals from the 12-Lead ECGs were manually read and confirmed by an external cardiologist/vendor. All ECGs were read blinded.

The sponsor comments: "A number of ECG readings failed first time so these were replaced with 'unscheduled' ECGs at that same time point. Programming was performed (based on each subjects' dosing time) to ensure that these unscheduled replacement ECG results were 'slotted in' to the relevant time-point for inclusion in the mean calculations described above. This resulted in some time points for some subjects having more than three ECG recordings if more replacements were done than number of ECGs that failed."

Reviewer's comment: The meaning of the sponsor's statement is unclear.

3.2.7 Sponsor's Results

3.2.7.1 Study Subjects

152 healthy subjects 18 – 55 years old with normal ECGs and BMIs were randomized. The original plan was to recruit 128 subjects so as to have a minimum of 50 subjects per arm completing the study. During conduct of the study additional subjects were recruited above the 128 in order to meet the 50 evaluable subjects per arm due to a larger than expected dropout rate. 19 withdrew sessions 1 or 2, during which moxifloxacin or its "placebo" were administered. 13 subjects withdrew while being administered LAMICTAL® and 13 while being administered LAMICTAL® placebo. Three subjects were withdrawn due to protocol violations, 12 due to AEs, 26 due to "subject decision," and 4 due to "other."

Reviewer's comment: The sponsor provides no reason for the high withdrawal rate.

3.2.7.2 Statistical Analyses

The primary variable of interest is the QTcF for each active regimen relative to placebo after baseline adjustment.

3.2.7.2.1 Primary Analysis

The Sponsor's statistical mixed model analysis was conducted on the manually read ECG data. The final primary analysis was a repeated measures mixed effects analysis of covariance model on manually read QTcF fitted with regimen and time point and regimen*time point as fixed effects with covariate Session 3 pre-treatment baseline and gender and pre-treatment baseline*time and subject as random. The differences of lamotrigine against placebo with corresponding 90% confidence intervals was calculated for each time point using the appropriate error term at days 42 (100mg), 63 (300mg) and 77 (400mg). The absence of QTcF prolongation for lamotrigine required that the upper limit of those confidence intervals across all time points be smaller than 10 ms.

To assess the assay sensitivity the largest time-matched mean difference in QTcF for the moxifloxacin group as compared to placebo was used. The repeated measures analysis was conducted for data from sessions 1 and 2 on moxifloxacin 400mg vs. Placebo. The differences of moxifloxacin 400 mg against placebo with corresponding 90% confidence intervals was calculated for each time point using the appropriate error terms. Assay sensitivity was concluded if the lower limit of the two-side 90% Confidence Interval for the largest time-match mean QTcF interval difference between Moxifloxacin and placebo exceeded 0 ms, and in addition the upper limit of this confidence interval exceeded 10 ms.

The results of the sponsor's analysis are graphically presented in **Figure 1** and summarized in Table 5.

Based on the above table, no prolongation of QTcF interval at steady state lamotrigine 50 mg, 150 mg or 200 mg bid compared with placebo was observed at any time point. All three doses' 90% confidence interval upper bounds at all time points excluded an effect ≥ 10 ms. Furthermore, the greatest difference in QTcF for moxifloxacin compared with placebo was observed at 2.5 h post dose. The 90% confidence interval at this time point demonstrates that the true mean difference could lie between 13.50 ms and 16.11 ms. The sensitivity of this study in assessing QT effects was thus confirmed.

Figure 1: Sponsor's Analysis: Mean (90% Confidence Intervals) ΔΔQTcF by Time for Each Treatment Group

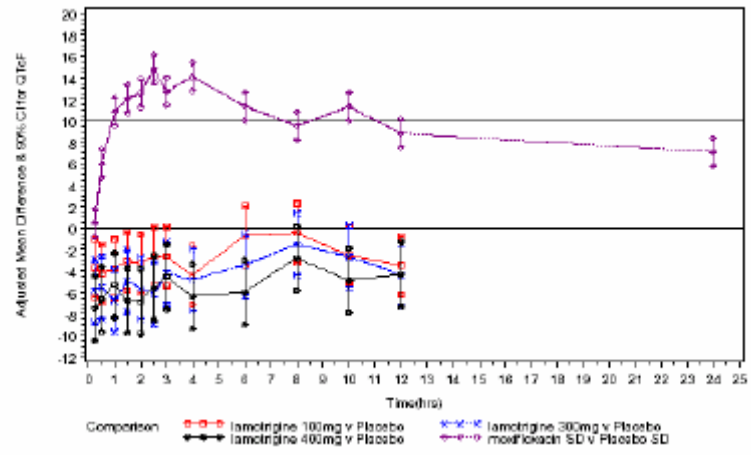


Table 5: Largest ΔΔQTcF across the Time Points and the Corresponding 90% Confidence Intervals

Statistics	Treatment Group			
	Lamotrigine 200mg bid	Lamotrigine 150mg bid	Lamotrigine 50mg bid	Moxifloxacin
Session	5 (Day 77)	4 (Day 63)	3 (Day 42)	1 and 2 (Day 1)
Sample Size (n)	49 vs. 57 for Pl*	51 vs. 58 for Pl	54 vs. 60 for Pl	141 vs. 145 for Pl
Time (hr)	8	8	8	2.5
Mean Diff (ms)	-2.81	-1.50	-0.45	14.81
90% CI (ms)	[-5.82, 0.20]	[-4.39, 1.39]	[-3.19, 2.29]	[13.50, 16.11]

[Reproduced from Table 13 and 14 of the submission] * Pl=Placebo

3.2.7.2.2 Categorical Analysis

The sponsor presented their categorical analysis by listing the frequencies of subjects with maximum post-dose QTcF values by different categories and results are summarized in Table 6. The frequency of subjects with maximum increases from baseline in QTcF by category is summarized in Table 7.

Table 6: Frequency of Subjects with Max Post-Dose QTcF (Sponsor)

Treatment Group	Post-Dose QTcF, msec			
	≤450	> 450	> 480	> 500
Session 1 / 2 (Day 1), n (% subjects)				
Moxifloxacin 400 mg single dose	140 (>99)	1 (<1)	0	0
Placebo single dose	145 (100)	0	0	0
Session 3 (Day 42), n (% subjects)				
Lamotrigine 50 mg bid	54 (100)	0	0	0
Placebo	60 (100)	0	0	0
Session 4 (Day 63), n (% subjects)				
Lamotrigine 150 mg bid	51 (100)	0	0	0
Placebo	58 (100)	0	0	0
Session 5 (Day 77), n (% subjects)				
Lamotrigine 200 mg bid	49 (100)	0	0	0
Placebo	57 (100)	0	0	0

Table 7: Sponsor's Analysis of Frequency of Subjects with Max increase from Baseline in QTcF

Treatment Group	Change in QTcF, msec		
	≤30	>30	>60
Session 1 / 2 (Day 1), n (% subjects)			
Moxifloxacin 400 mg single dose	118 (84)	23 (16)	0
Placebo single dose	144 (>99)	1 (<1)	0
Session 3 (Day 42), n (% subjects)			
Lamotrigine 50 mg bid	53 (98)	1 (2)	0
Placebo	59 (98)	1 (2)	0
Session 4 (Day 63), n (% subjects)			
Lamotrigine 150 mg bid	49 (96)	2 (4)	0
Placebo	57 (98)	1 (2)	0
Session 5 (Day 77), n (% subjects)			
Lamotrigine 200 mg bid	48 (98)	1 (2)	0
Placebo	55 (96)	2 (4)	0

3.2.7.3 Safety Analysis

No deaths occurred during the study. One SAE, pulmonary tuberculosis, is reported. Of the 12 AEs that led to subject withdrawal, 3 occurred during the 2 sessions in which moxifloxacin or its "placebo" was administered. 2 occurred in subjects randomized to LAMICTAL® placebo. Of the seven AEs that occurred during LAMICTAL® administration and resulted in withdrawal of the subjects, 3 were rashes, 1 was an increase in LFTs, 1 was otitis media, 1 was pleuritic chest pain, and 1 was abdominal pain associated with hypotension.

Two episodes of syncope are reported; both occurred in subjects while taking moxifloxacin. The only cardiac AEs reported in subjects administered LAMICTAL® were two episodes of palpitations. One occurred while a subject was taking LAMICTAL® 25 mg bid and the other on 200 mg bid.

3.2.7.4 Clinical Pharmacology

3.2.7.4.1 Pharmacokinetic Analysis

The concentrations of lamotrigine were dose-dependent as expected across 50 mg, 150 mg and 200 mg bid doses as shown in Table 8.

Table 8: Sponsor's Table: Mean Lomotrigine PK Parameters

Treatment	N	AUC(0–12)[1] (µg.h/mL)	Cmax[1] (µg/mL)	tmax[2] (h)
Lamotrigine 50 mg bid	54	25.7 (40.7)*****	2.59 (38.3)	1.12 (0, 4.12)
Lamotrigine 150 mg bid	52	69.6 (27.4)*	7.22 (24.7)***	1.08 (0.33, 3.08)***
Lamotrigine 200 mg bid	51	93.0 (23.5)**	9.61 (20.5)**	1.58 (0.33, 4.08)**
Moxifloxacin 400 mg[5]	142[4]	24100[3] (18.5)****	2280 (26.0)	1.60 (0.35, 6.10)

Source Data: Tables 12.1-12.4. N = number in population. * n = 50, ** n = 49, *** n = 51, **** n = 141, ***** n = 52.

1. Geometric mean (%CV).
2. Median (range).
3. AUC(0–24).
4. Subject 800149 was excluded as they vomited immediately after dosing and then withdrew from the study.
5. Concentration in ng/mL.
6. Note all AUC(0–12) values on lamotrigine 50 mg bid were extrapolated from the 10 h nominal time point because the 12 h samples were taken after the second lamotrigine dose).

bid = twice-daily.

3.2.7.4.2 Exposure-Response Analysis

For lamotrigine, the PK/PD model showed that there was a statistically significant decrease in the individually corrected QT interval over the concentration range studied ~ 0–14,200 ng/mL. The slope was predicted to be -1.01 ms/1000 ng/mL in males and -1.05 ms/1000 ng/mL in females. This corresponds to an approximate 14.9 ms decrease in individually heart rate corrected QT at the upper end of the concentration range studied.

Figure 2: Sponsor's Figure: Concentration-QTcI for Lamotrigine in Males

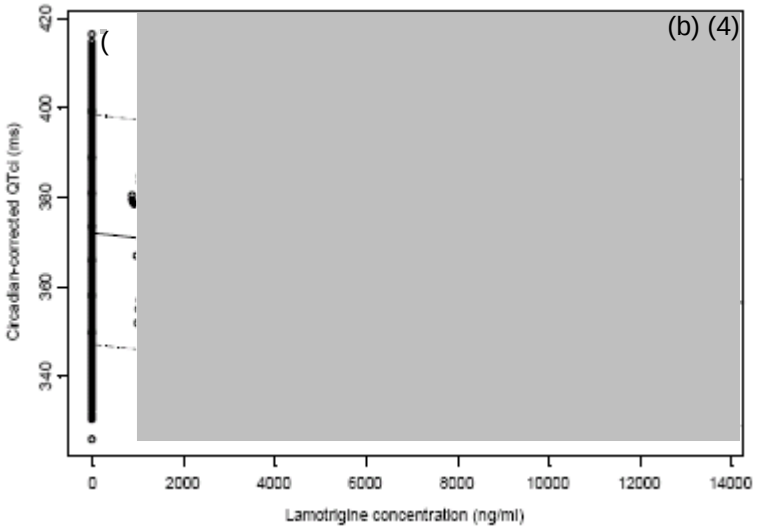
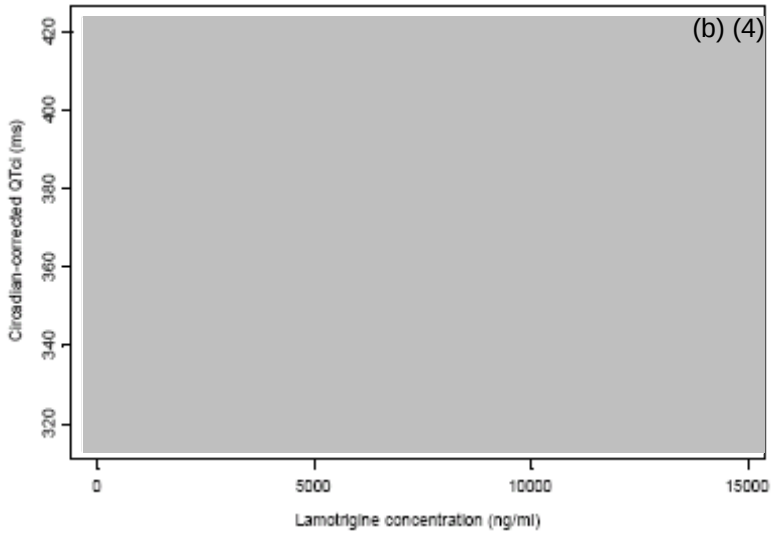


Figure 3: Sponsor's Figure: Concentration-QTcI for Lamotrigine in Females



Reviewer's Comment: The sponsor's analysis is misleading and should not be used for inferences pertaining to concentration-QTc relationships.

4 REVIEWERS' ASSESSMENT

4.1 STATISTICAL ASSESSMENTS

Primary Analysis

This section contains the results of this statistical reviewer's analysis of the primary endpoint, change from baseline to each of 5 sessions in QTcF, denoted as ΔQTcF. This reviewer also used the Analysis of Covariance (**ANCOVA**) to analyze **ΔQTcF**, at each time point. The objective was to compare Lamotrigine with placebo.

Point estimates and 90% confidence intervals for the adjusted mean difference in QTcF at each time point are shown in Table and Table 10 for lamotrigine at doses of 50, 150 and

200 mg bid vs. placebo and for single-dose moxifloxacin 400 mg vs. single-dose placebo. Based on these two tables:

- For Lamotrigine 200 mg bid: (a) at no time point the Upper Limit of the 90% Confidence Interval (**UL-90%-CI**) exceed 10 ms; (b) the maximum difference occurs at 8-hour, with a point estimate of ΔQTcF = -3.39 ms and UL-90%-CI = -0.41 ms, and (c) the numerical values at time-match points are similar to the sponsor's results.
- For Lamotrigine 150 mg bid: (a) at no time-match point the Upper Limit of the 90% Confidence Interval (**UL-90%-CI**) exceed 10 ms; (b) the maximum difference occurs at 8-hour, with a point estimate of ΔQTcF = -1.50 ms and UL-90%-CI =1.37 ms, and (c) the numerical values at time-match points are similar to the sponsor's results. .
- For Lamotrigine 50 mg bid: (a) at no time-match point the Upper Limit of the 90% Confidence Interval (**UL-90%-CI**) exceed 10 ms; (b) the maximum difference occurs at 8-hour, with a point estimate of ΔQTcF = -0.38 ms and UL-90%-CI =2.36 ms, and (c) the numerical values at time-match points are similar to the sponsor's results.

In conclusion, no prolongation of the QTcF at steady state lamotrigine 50 mg, 150 mg or 200 mg bid compared with placebo was observed at any time point.

Table 9: Point Estimates and 90% CIs for the Adjusted Mean Difference in QTcF (Lamotrigine 200 mg bid and Moxifloxacin 400 mg)

Time point, h	Lamotrigine 200 mg bid Vs. Placebo (Day 77)		Single-Dose Moxifloxacin 400 mg Vs. Single-Dose Placebo (Session 1/2)	
	Point Estimate	90% Confidence Interval	Point Estimate	90% Confidence Interval
0.25	-7.67	(-10.64, -4.69)	0.48	(-1.03, 1.99)
0.5	-6.74	(-9.71, -3.78)	6.05	(4.54, 7.57)
1	-5.31	(-8.28, -2.33)	10.52	(9.55, 12.17)
1.5	-6.72	(-9.79, -3.76)	11.98	(10.76, 13.49)
2	-6.71	(-9.67, -3.75)	12.27	(10.77, 13.79)
2.5	-5.77	(-8.73, -2.81)	14.54	(13.03, 16.05)
3	-4.98	(-7.93, -2.01)	12.92	(11.41, 14.43)
4	-6.39	(-9.35, -3.43)	13.96	(12.45, 15.46)
6	-5.75	(-8.71, -2.79)	11.54	(10.02, 13.05)
8	-3.39	(-6.36, -0.41)	9.15	(7.63, 10.66)
10	-5.01	(-7.97, -2.05)	11.07	(9.56, 12.59)
12	-4.31	(-7.29, -1.34)	8.64	(7.12, 10.15)
24	-	-	7.00	(5.48, 8.51)

[Source: FDA Reviewer's analysis result]

Table 10: Point Estimates and 90% CIs for the Adjusted Mean Difference in QTcF (Lamotrigine 150 mg bid and 50 mg bid)

Time point, h	Lamotrigine 150 mg bid Vs. Placebo (Day 63)		Lamotrigine 50 mg bid Vs. Placebo (Day 42)	
	Point Estimate	90% Confidence Interval	Point Estimate	90% Confidence Interval

0.25	-5.98	(-8.88, -3.09)	-4.08	(-6.81, -1.35)
0.5	-5.55	(-8.34, -2.58)	-4.23	(-6.97, -1.51)
1	-6.91	(-9.78, -4.03)	-3.62	(-6.35, -0.88)
1.5	-4.80	(-7.66, -1.93)	-2.82	(-5.55, -0.09)
2	-5.62	(-8.49, -2.76)	-3.23	(-5.97, -0.51)
2.5	-6.87	(-8.74, -2.99)	-2.36	(-5.09, 0.36)
3	-4.12	(-6.99, -1.26)	-2.82	(-5.56, -0.10)
4	-5.00	(-7.88, -2.13)	-4.52	(-7.25, -1.79)
6	-3.39	(-6.26, -0.51)	-1.05	(-3.81, 1.70)
8	-1.50	(-4.38, 1.37)	-0.38	(-3.12, 2.36)
10	-2.88	(-5.75, -0.02)	-2.54	(-5.27, 0.19)
12	-4.14	(-7.01, -1.46)	-3.55	(-6.27, -0.82)

[Source: FDA Reviewer's analysis result]

Assay Sensitivity Analysis

Same ANCOVA, as performed for the primary analysis, was performed to assess the assay sensitivity. Results are summarized in Table and show that: (a) at largest time-matched mean QTcF, the lower limit of 90% CIs (LL-90%-CI) exceed 5 ms and UL-90%-CIs exceed 10 ms; (b) maximum ΔΔQTcF occurs at time point 2.50-hour; (c) the numerical results at time point 2.50-hour, namely, point estimate ΔΔQTcF =14.54 ms**,** LL-90%-CI = 13.03 ms, and UL-90%-CIs = 16.05 are similar to those reported by the sponsor. However, sponsor did not adjust for multiple endpoints in the assay sensitivity analysis. We did Bonferroni correction for the 13 time points and at least at 10 time points, the lower 95% CI (after multiple endpoint adjustment) is above 5 ms. In fact, the lower limit at time point 2.5 hour is 11.88 ms.

Categorical Analysis

No subject's QTcF is above 450 ms at baseline. Three subjects' QTcF after administration of moxifloxacin is above 450 ms. No subject's QTcF after administration of lamotrigine is above 450 ms (Table 11). Almost half of moxifloxacin subjects' had a change in QTcF from baseline between 30 ms and 60 ms whereas only a few lamotrigine subjects did (Table 1). One moxifloxacin subject and no lamotrigine subjects had a change in QTcF from baseline between greater than 60 ms (Table 13).

Table 11: Frequency for QTcF > 450 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline- Moxi 400 mg	142	0	0.00	1287	0	0.00
Baseline- Lam 200 mg Bid	49	0	0.00	431	0	0.00
Baseline- Lam 150 mg Bid	51	0	0.00	468	0	0.00
Baseline- Lam 50 mg Bid	54	0	0.00	492	0	0.00
Baseline- Placebo Session 1-2	145	0	0.00	1302	0	0.00
Baseline-Placebo Session 3-5	60	0	0.00	580	0	0.00
Moxifloxacin 400 mg	142	3	2.11	5492	7	0.13

Lam 200 mg Bid	49	0	0.00	1746	0	0.00
Lam 150 mg Bid	51	0	0.00	1843	0	0.00
Lam 50 mg Bid	54	0	0.00	1981	0	0.00
Placebo Session 1/2	145	0	0.00	5714	0	0.00
Placebo Session 3-5	60	0	0.00	2338	0	0.00

Table 1: Frequency for ΔQTcF: 30 - 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Moxi 400 mg	142	65	45.77	5499	198	3.6
Lam 200 mg Bid	49	3	6.12	1746	15	0.86
Lam 150 mg Bid	51	6	11.76	1843	11	0.60
Lam 50 mg Bid	54	6	11.11	1981	7	0.35
Placebo Session 1-2	145	14	9.66	5714	22	0.39
Placebo Session 3-5	60	7	11.67	2338	7	0.30

Table 13: Frequency for ΔQTcF > 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Moxi 400 mg	142	1	0.7	5499	1	0.02
Lam 200 mg Bid	49	0	0.00	1746	0	0.00
Lam 150 mg Bid	51	0	0.00	1843	0	0.00
Lam 50 mg Bid	54	0	0.00	1981	0	0.00
Placebo Session 1-2	145	0	0.00	5714	0	0.00
Placebo Session 3-5	60	1	1.67	2338	1	0.04

4.2 CLINICAL PHARMACOLOGY ASSESSMENTS

Individual RR correction did not account for all the variability in QT. QTcI and QTcB, as shown in Figure 4 are biased with respect to correction for RR while QTcF appears to be the least biased. The time courses of the mean change in QTcF and concentrations for the various treatment groups are shown in Figure 5.

The relationship between concentration-QTcF across a wide concentration range, as shown below in Figure 6, is flat or at most shallowly negative. This observation validates the E14 analysis. The maximum mean changes at 50, 150 and 200 mg doses are -4.41, -6.76 and -7.48 ms, respectively. A 3-fold increase in dose from 50 mg to 150 mg resulted in a further decrease in QTcF by 2.2 ms.

Figure 4. FDA Analysis: Baseline day QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).

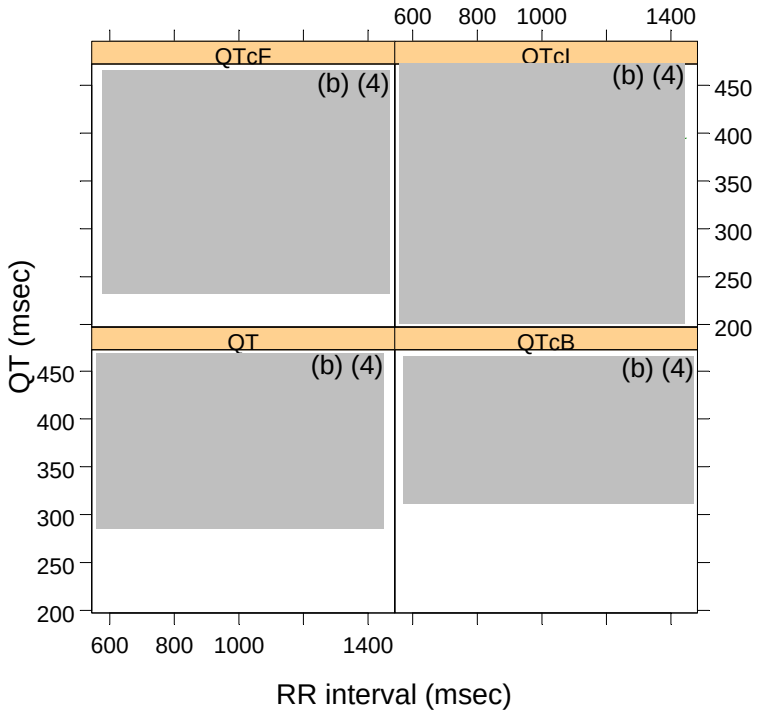


Figure 5. FDA Analysis: Mean ΔΔQTcF and Lamictal concentration-time profiles for 300 mg/day (blue line) and 400 mg/day (red line). Together with Moxifloxacin 400 mg (green line).

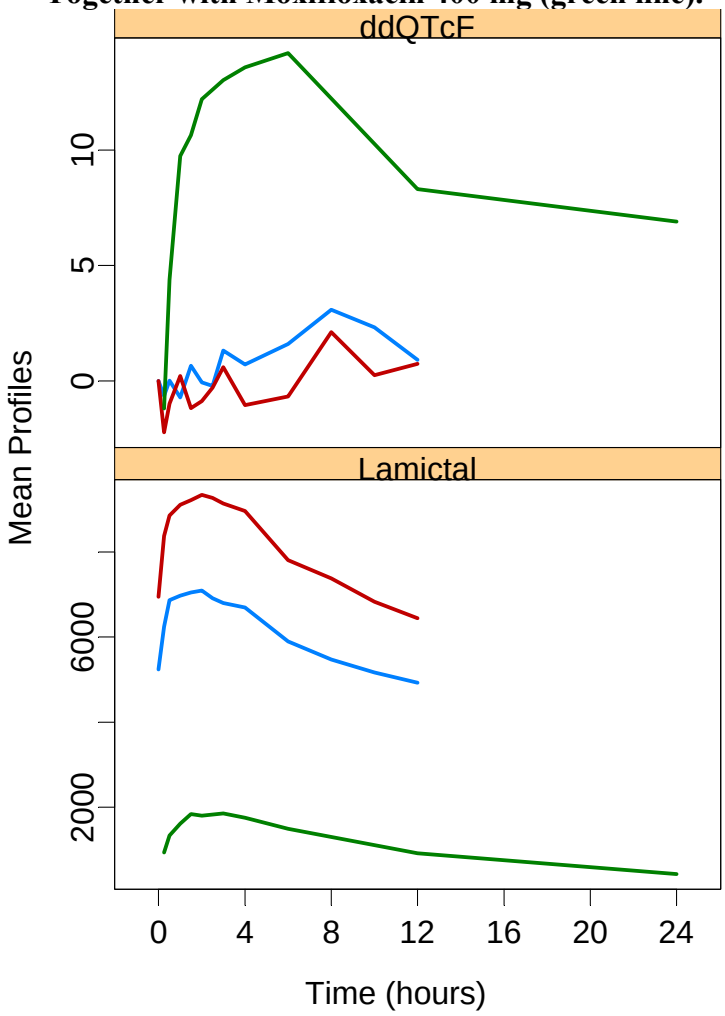
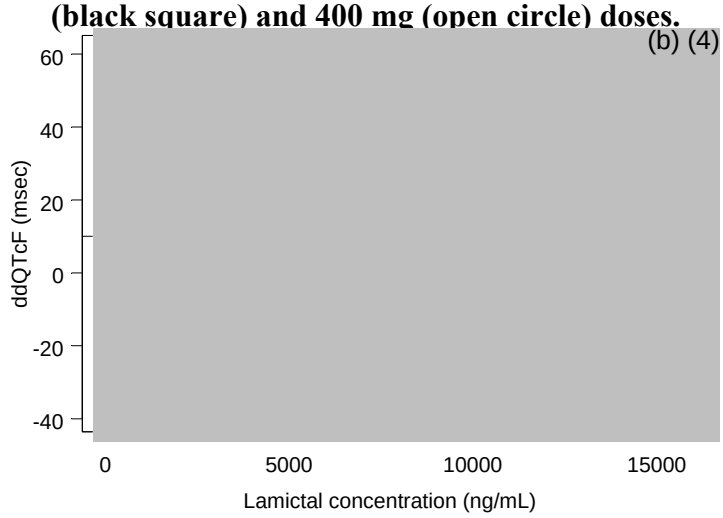


Figure 6. FDA Analysis: Relationship between ΔΔQTcF (change from baseline and placebo adjusted QTcF) and Lamictal concentrations 300 mg (black square) and 400 mg (open circle) doses.



4.3 CLINICAL ASSESSMENTS

None of the adverse events identified as significant in the ICH E14 guidelines (i.e., sudden death, torsade de pointes, ventricular tachycardia, syncope, and seizures) were observed occurring in any subject administered LAMICTAL® during the trial.

5 APPENDIX

5.1 TABLE OF STUDY ASSESSMENTS

Procedure	Sessions 1 and 2 (Days -1 to 1)	Session 3 (Days -1-42)	Session 4 (Days 43-63)	Session 5 (Days 64-77)	Down- titration (Days 78-85)
Visit to Unit [a]	In patient: from evening of Day -1 until Day 1 +24h post-dose	In-patient: Day -1 until Day 1 +12h post-dose Out-patient (12h): Days 8, 15, 22, 29, 36. In-patient: D41pm – D42 +12h. Day 40 outpatient	Out-patient (12h): Days 50, 57. In-patient: D62pm onwards.	In-patient until Day 77 +12h.	Out-patient: Days 80, 82, 84, 85.
Alcohol Screen	Day -1	D1, 8, 15, 22, 29, 36, 41	Days 50, 57, 62	Days 70, 76	D80, 82, 85
Urine hCG (in females)	Day -1	D1, 8, 15, 22, 29, 36, 41	Days 50, 57, 62	Days 70, 76	D80, 82, 85
Con. Med. review	Day -1	D1, 8, 15, 22, 29, 36, 41	Days 50, 57, 62	Days 70, 76	D80, 82, 85
Undeclared drugs	Day -1	D1, 8, 15, 22, 29, 36, 41	Days 50, 57, 62	Days 70, 76	D80, 82, 85
Adverse event reporting	Days -1 & 1: pre-dose, 4 and 12 hours post-dose	D1, 8, 15, 22, 29, 36, 41 Day 42: pre-dose, 4 and 12 hours post-dose	Days 50, 57, 62 Day 63: pre-dose, 4 and 12 h post-dose	Days 70, 76 Day 77: pre-dose, 4 and 12 h post-dose	D80, 82, 85 pre-dose
Serial 12-lead ECG [b]	Day 1: Pre-dose (-1h, -30m, -5m), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24h post-dose	Day 1: Pre-dose (-1h, -30m, -5m) Day 42: Pre-dose (-1h, -30m, -5m), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12h post-dose	Day 63: Pre-dose (-1h, -30m, -5m), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12h post-dose	Day 77: Pre-dose (-1h, -30m, -5m), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12h post-dose	Day 85: pre-dose
Vital signs [supine/standing]	Day 1: Pre-dose, 2, 8, 22-24 h post-dose	Day 42: Pre-dose, 2, 8, 22-24 h post-dose	Day 63: Pre-dose, 2, 8, 22-24 h post-dose	Day 77: Pre-dose, 2, 8, 22-24 h post-dose	Day 85: pre-dose

Clinical laboratory	Day -1	Day 42: pre-dose	Day 63: pre-dose	Day 77: pre-dose	Day 85: pre-dose
Drug administration	See Table 5	See Table 5	See Table 5	See Table 5	See Table 5
Pharmacokinetic sampling	Moxifloxacin/placebo Day 1: pre-dose, 0.25, 0.50, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 12, 24h post-dose	Lamotrigine/placebo D42: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12h post-dose	Lamotrigine/placebo D63: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12h post-dose	Lamotrigine/placebo D77: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12h post-dose	Not applicable
Pre-dose PK	Not applicable	Days 40, 41: pre-morning-dose	Days 61, 62: pre-morning-dose	Days 75, 76: pre-morning-dose	Not applicable
PGx (if consented)	Session 1 D1 pre-dose	Not applicable	Not applicable	Not applicable	Not applicable

a. Out-patient clinic visits, subjects will attend the clinic for dosing with breakfast.
b. 12-Lead ECGs must be obtained prior to any other assessment scheduled, following immediately by vital signs and PK blood draws. ECG measurements are taken in triplicate approximately 1 minute apart. Pre-dose ECG assessments are taken immediately prior to the dosing of study medication.

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