CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	22115
Priority or Standard	Standard
Submit Date(s)	3/31/2010
Received Date(s)	3/31/2010
PDUFA Goal Date	1/31/2011
Division / Office	DNP
Reviewer Name(s)	Steven T. Dinsmore
Review Completion Date	
Established Name	Lamotrigine
(Proposed) Trade Name	Lamictal XR
Therapeutic Class	Anticonvulsant
Applicant	GSK
Formulation(s)	XR = extended release
Dosing Regimen	Oral, once daily
Indication(s)	Conversion to monotherapy
Intended Population(s)	Adults and Children age 13 and above receiving treatment with a single AED

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

It is also noted that advisory committee was convened on March 10, 2011 to advise on the validity of the historic controlled methodology of the pivotal study LAM30055 and the adequacy of this study to support the efficacy of LAMICTAL XR monotherapy. The committee agreed that historic control methodology utilized by French et al. is an acceptable method and the majority agreed that the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy treatment.

1.2 Risk Benefit Assessment

Lamotrigine has established efficacy in epilepsy treatment and the immediate release form is currently approved for conversion to monotherapy in patient's receiving treatment with a single AED. Availability of the extended release form would be of benefit to those patients currently taking Lamictal XR who are candidates to switch to monotherapy. There is no new risk related to the active ingredient that has not already been identified by the extensive experience with immediate release lamotrigine. Additional benefit may be anticipated from greater ease of compliance with a Lamictal XR monotherapy dosing program.

This application was supported by study LAM30055 where a dose of 300mg/day Lamictal XR compared to historic control was the primary endpoint. This dose is lower than the approved monotherapy dose for LTG IR of 500mg/day (250mg twice a day). The data from study LAM30055 reveal that the escape rate for both LTG XR 300mg and 250mg is less than the lower bound prediction interval in both of the sensitivity analysis performed by the FDA statistician. In addition the sponsor provides additional support by the observation that LTG IR at 150mg / day has shown efficacy similar to CBZ 600mg/day, LTG IR dose was also chosen in a study where LTG !R was given concurrently with background EIAEDs during transition to LTG IR monotherapy. In the conversion interval, when the effective dose of lamotrigine approximated 250mg/day, superiority over the pseudoplacebo treatment arm was observed. Overall the efficacy findings of study LAM30055 and the supportive arguments by the sponsor indicate the 250mg to 300mg/ day dose are adequately effective as monotherapy treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Medication guide dispensed with each LAMICTAL prescription with REMS assessment using a survey of patient understanding of serious LAMICTAL risks at 18 months, 3 years and 7 years.

1.4 Recommendations for Postmarket Requirements and Commitments

none

2 Introduction and Regulatory Background

2.1 Product Information

LAMICTAL® (lamotrigine, LTG), a phenyltriazine anticonvulsant, was first approved in the United States (US) in December 1994 (New Drug Application [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 also 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. More recently, LAMICTAL was approved for primary generalized tonic-clonic (PGTC) seizures in September 2006 in adults and pediatric subjects (2-16 years of age).

An extended-release (LTG XR) formulation of lamotrigine (NDA 22-115; LAMICTAL Extended-Release Tablets) is currently approved for use as adjunctive therapy of partial seizures and PGTC seizures in patients thirteen years and older. The current application seeks approval of LTG XR for conversion to monotherapy in subjects ≥13 years of age with partial seizures at target maintenance doses of 250mg to 300mg / day

2.2 Tables of Currently Available Treatments for Proposed Indications

This topic has been fully covered in the application for Lamictal XR for adjunctive treatment of primary generalized tonic-clonic seizures (NDA 22509)1

1. Dinsmore S. Medical Officer Review, NDA22509. Product: Lamictal XR, Indication: Oral, once daily adjunctive treatment for primary generalized tonic clonic (PGTC) seizures. 1/28/2010

2.3 Availability of Proposed Active Ingredient in the United States

Lamotrigine is approved in the US as immediate release and extended release forms for several indications noted in section 2.1

2.4 Important Safety Issues with Consideration to Related Drugs

Lamotrigine (LAMICTAL, 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine and is chemically unrelated to other marketed anitiepileptic drugs (AEDs). The precise mechanism(s) by which lamotrigine exerts its anticonvulsant effects is unknown. In vitro pharmacologic studies suggest that lamotrigine inhibits voltage sensitive sodium channels thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (primarily glutamate and aspartate).

Neurobiology of-Modulation of the gating of brain sodium channels is believed to account, at least in part, for the ability of several other AEDs to protect against generalized tonic-clonic and partial seizures. These AEDs include phenytoin, carbamazepine, oxcarbazepine and zonisamide, and possibly felbamate, topiramate and valproate[2].

Although lamotrigine may share sodium channel action with several other anticonvulsants the chemical moiety is unrelated and there is no overlap of major unique safety issues with these other sodium channel modulators. There is overlap in the common anticonvulsant adverse effects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The unique regulatory issue of this submission is the absence of an internal control. The drug recipient test group of the pivotal trial for this submission is compared to an historical control group. This historic control method is fully discussed in section 6. On July 24, 2009 there was a teleconference between the FDA and representatives of GlaxoSmithKline to discuss GSK plans for this sNDA (use of Lamictal XR for conversion to monotherapy). GSK proposed use of an historic control devised based on a White Paper by French et.al. At this meeting the FDA stated “a single clinical study using a historic control could potentially be sufficient to support approval for monotherapy of partial onset seizures after having previously been determined to be effective by adequate and well controlled clinical trials for adjunctive treatment. Lamictal XR has been approved as adjunctive therapy in adults with partial seizures. Therefore, a single clinical study using a historic control might be sufficient to support approval of LTG XR for conversion to monotherapy in adults with partial seizures.

2 Rogawski MA, Löscher W. The Neurobiology of Antiepileptic Drugs. Nature Reviews Neuroscience 2004;5(7):553-564.

Whether the recently completed study LAM30055 will be adequate to support approval will be a review issue at the time of NDA submission"

No SPA for this development plan was submitted.

2.6 Other Relevant Background Information

The historic control monotherapy methodology presented in the White Paper and in the published version, "Historical control monotherapy design in the treatment of epilepsy"[3] springs from a concern that patient safety is compromised in the traditional path to approval for monotherapy. Most approvals for monotherapy have been achieved using a trial design known as the "pseudo-placebo withdrawal to monotherapy study", which assigns treatment resistant patients to receive study drug or a suboptimal maintenance dose of a safe and effective active drug. Those in the pseudoplacebo arm of the study are at risk of breakthrough seizure.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The reviewer is concerned about two patients with SAEs identified in the LAM30055 study report (Table 26) and the summary of clinical safety (Table 24) (SCS). In both cases a traumatic event was apparently the primary reason for the designation of "serious" adverse event. In Patient #62 the event was "trauma craniocerebral", in the second case, patient # 810 the event was "possible concussion". In both cases the underlying cause of these traumas was a seizure. The causative basis of seizure was not indicated in the discussion section or tables of non-lethal serious adverse events. This is a deficiency in an anticonvulsant study where knowledge of the frequency of epilepsy related adverse events is always important.

The fields from the serious adverse events section of the case report forms for both patients are shown below. The relationship of the trauma to seizure is noted in the "general narrative comment" field. It should be intuitive in the construction of a study report or summary of clinical safety for an anticonvulsant study that involvement of a seizure in a serious adverse event should be prominent in discussion or included in the table of serious adverse events.

Patient ID 62:

3 French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. Epilepsia 2010;51(10):1936-1943

FIELD 4a: Serious Adverse Event- trauma craniocerebral
FIELD 5: Specify the reason for considering this an SAE-
Is life-threatening Requires hospitalization or prolongation of existing hospitalization
FIELD 12: General narrative comments: head injury as a result of seizure; hospitalization

Patient 810:

FIELD 4a: Serious Adverse Event- Possible Concussion
FIELD 5: Specify the reason for considering this an SAE-
Requires hospitalization or prolongation of existing hospitalization
FIELD 12: General narrative comments: Subject was in a motor vehicle accident while having a seizure. He was admitted into the hospital because of a possible concussion, and the seizure.

3.2 Compliance with Good Clinical Practices

The sponsor identified a site with systematic protocol violations. A site in Costa Rica, #27083 was not using the study drug prescription forms and was not properly maintaining the bulk drug accountability log. Return of used drug by subjects was also not being recorded consistently. In addition placebo which was used as blinding instrument to balance pill count was no used in a consistent manner. As a result, dosing errors may have occurred for some subjects, including errors during the period of dose escalation. Because the record keeping did not a allow GSK to pinpoint problems with specific subjects, it was decided to exclude all data from all subjects at this site from the per protocol analysis but data from this site was retained in the ITT analysis.

Our statistical reviewer was appraised of that the sponsor retained site 027083 in the ITT analysis and was asked to re-analyze the efficacy results of the ITT population with this site removed. She found that with this site removed the ITT population analysis still remained below the lower bound of the prediction interval.

Three sites for DSI inspection from study LAM30055 were selected, one from the Ukraine due to a large influence on the primary outcome measure, a second from the US, representing the largest US enrollment and with 2 protocol violations and the third from Argentina, also with a large influence on the primary outcome measure.

The Argentine site was found to have several protocol violations and study site procedural violations. For two patients there was failure to report adverse events. An additional two patients received incorrect total daily doses of study drug for a five week period. In each case the dose was lower than protocol directed dosing. Proper medication dosing records were not kept on all subjects. Randomization was assigned without waiting for a fax of the “randomization confirmation form”. Due to concerns about reliability of data from this site the statistical reviewer was requested to perform a

sensitivity analysis of LAM30055 efficacy results with this site excluded. The statistical reviewer found that the study results were not changed by exclusion of this site.

3.3 Financial Disclosures

None of the investigators in study LAM30055 had disclosable financial interests at initiation of their study participation. The sponsor does note that 12 (2.4%) of investigators did not have financial disclosure update information available when needed for documentation at the time of this NDA. The sponsor does note that "based on information available internally, none of the clinical investigators listed below had disclosable interests.

Reviewer comment: According to the sponsor the absent information is update information with no conflict present for these investigators initially. Although 21 CFR part 54 requires update of financial disclosure during the study and up to 1 year after completion for investigators whose disclosure status changes to meet disclosure requirements, this section does not require spontaneous re-update of information. In the event that any of these 12 investigators had an unreported change in status with potential influence, their influence will be limited because none are principle investigators and there is not more than one of these investigators at a site.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

N/A for this application

4.2 Clinical Microbiology

N/A for this application

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical data have been generated for LTG XR.

4.4 Clinical Pharmacology

The PK and drug interactions of LTG, administered as the IR tablet has been well established (NDA 20-241, approved December 1994). These data are summarized in the prescribing information for LTG XR [LAMICTAL XR Extended-Release Tablets Package Insert, 2009]. No further PK or drug interactions studies were conducted to support this application.

4.4.1 Mechanism of Action

N/A

4.4.2 Pharmacodynamics

N/A

4.4.3 Pharmacokinetics

N/A

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Table of White Paper Monotherapy Trials Including LAMICTAL IR (study 30/31) and LAMICTAL XR (study LAM30055)

Study[1]	N	Mean Age (years) (range)	Gender (%, M/F)	Study Locations	Race (%) (White/Black/ Other)
1	94	35 (14-63)	54:45	US, Canada	NA
2 (US 30/31)	80	36 (14-71)	40:60	US	69/14/18
3	24	35 (NA)	38:63	NA	83/4/13
4	32	NA	NA	NA	NA
5	45	35 (18-53)	53:47	US	87/--/13
6	46	36 (11-66)	41:59	US	NA
7	22	38[2] (18-62)	NA	US	NA
8	55	35 (17-67)	36:64	NA	85/9/5
LAM30055 300 mg/day	112	34 (13-80)	50:50	US, Latin America, Ukraine, Russia, Korea	86/4/10
250 mg/day	111	33 (13-59)	59:41		86/4/10

5.2 Review Strategy

Create as discussion unfolds

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Study LAM30055

This was a double-blind, randomized, historic-control study comparing the premature discontinuation rate for 2 doses of LTG XR (300 and 250mg/day) to an historic escape rate determined from aggregated pseudoplacebo data [French, 2005]. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy lamotrigine dose than the currently-approved 500mg/day in subjects with partial epilepsy who were receiving AED monotherapy with VPA or a non-enzyme inducing AED (non-EIAED) but were still experiencing partial seizures. The study used a conversion to monotherapy design in which eligible subjects had LTG XR added to their current therapy (background AED) followed by gradual withdrawal of the background AED.

Screen and Baseline

Subjects who met eligibility requirements during screening entered an 8-week, non-interventional Baseline Phase to establish a 28-day baseline seizure frequency. Adequately documented historic seizure data and AED dosing information could be substituted for up to the first 4 weeks of baseline data with approval from GSK.

The baseline seizure frequency criterion was ≥4 partial seizures with ≥1 seizure occurring in each 28-day interval of the 8-week Baseline Phase. Subjects who did not meet this criterion (Baseline Failures) were allowed to enter the Continuation Phase for up to 24 weeks, if clinically appropriate.

Double Blind Treatment Phase

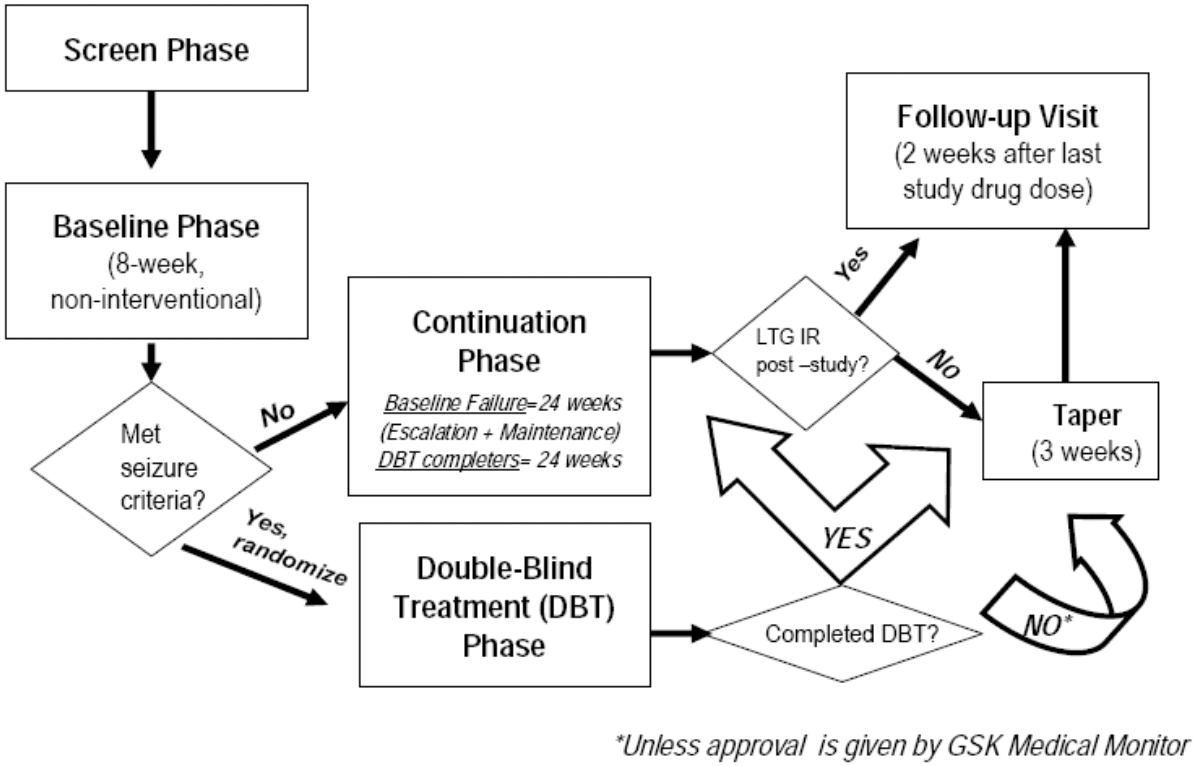
Subjects who met the baseline seizure criterion entered the Double-Blind Treatment Phase and were randomized (1:1) to receive LTG XR at either 300mg or 250mg given once daily. During the Conversion Phase, subjects underwent escalation to the LTG XR target dose and gradual withdrawal of the background AED. Subjects started the 12-week Monotherapy Phase when withdrawal of the background AED was complete.

No new AEDs could be added during the Baseline or Double-Blind Treatment Phases. Chronic benzodiazepine use for epilepsy management was prohibited, but acute benzodiazepine use as rescue medication was allowed with restrictions.

Continuation Phase

All enrolled subjects could participate in the open-label Continuation Phase, if appropriate. The Continuation Phase consisted of up to 24 weeks of additional monotherapy with LTG XR to allow for gathering additional, long-term safety information.

Figure 1 LAM30055 Study Design Schematic



Abbreviations: DBT = double-blind treatment; LTG = lamotrigine; IR = immediate-release; GSK = GlaxoSmithKline

Figure 2 LAM30055 LTG Escalation and Background VPA taper schedule (Subjects on background VPA)

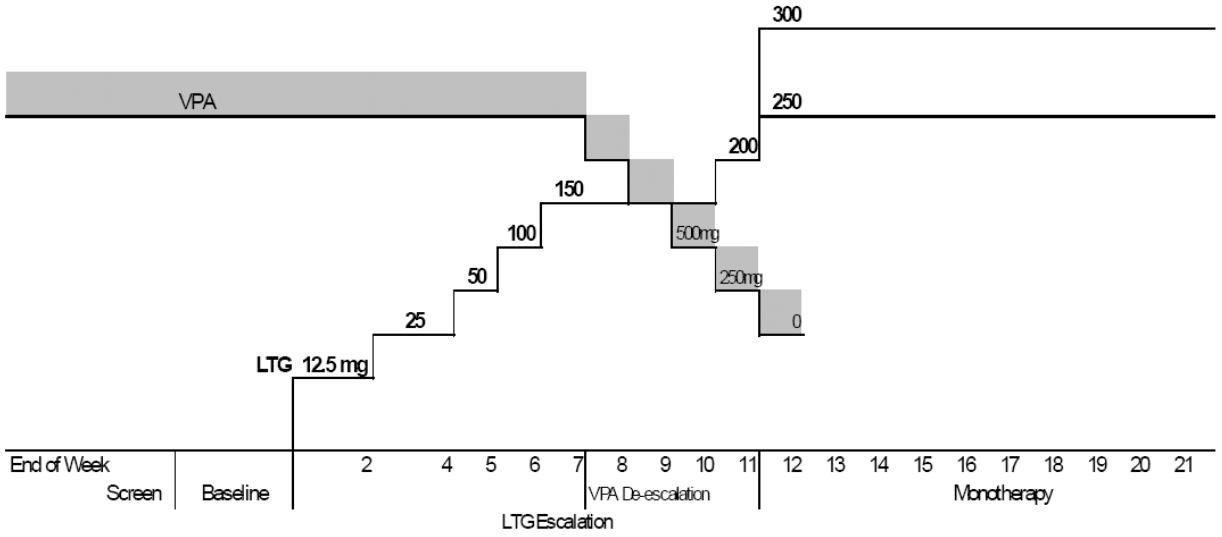
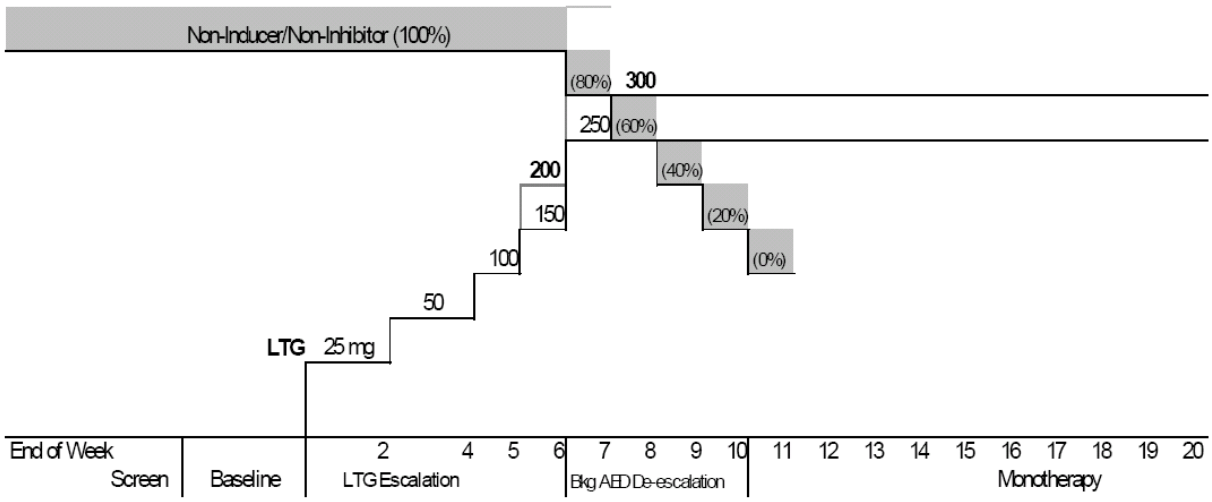


Figure 3 LAM30055 LTG Escalation and Background AED taper schedule (Subjects receiving neither VPA nor an EIAED)



Study Population

Inclusion Criteria

1. Male or female ≥ 13 years of age
2. Confident diagnosis of epilepsy with partial seizures for at least 24 weeks prior to baseline phase
3. documented history of partial seizures and the investigator had judged that the subject was likely to have at least 4 partial seizures during the 8 week baseline phase.

4. had experienced at lest 4 partial seizures (i.e., simple or complex partial seizures with or without secondary generalization) during an 8 week prospective baseline phase with at least one partial seizure occurring during each 4 week period. Note: with prior authorization from GSK, retrospective data could take the place of up to the first 4 weeks of the baseline phase for subjects providing reliable documentation of the following

a. a complete daily seizure diary that included the number, and type (i.e., simple or complex partial seizures with or without secondary generalization) of seizures experienced each day for up to 28 consecutive days immediately prior to the prospective Baseline Phase.
b. stability of prescribed dosages of background AED.
c. compliance with background AED.

All subjects permitted to use retrospective baseline data must have completed a minimum of 4 weeks (i.e., 28 days) of the prospective Baseline Phase. The retrospective plus the prospective Baseline Phases must equal the 56 consecutive days prior to start of dosing with study drug.
5. Was currently receiving AED monotherapy treatment with a stable regimen for at least 4 weeks prior to starting the Baseline Phase.
6. Was able and willing to maintain an accurate, complete, written daily seizure diary, or had a parent/caregiver who was able and willing to maintain an accurate, complete, written daily seizure diary for the entire duration of the study.
7. was able to comply with dosing of study drugs, background AED, and all study procedures.
8. Understood and signed written informed consent, or had a parent or a legally authorized representative who had done so, prior to the performance of any study assessments.
9. If female, and of childbearing potential, was using an acceptable form of birth control, to include one of the following: * see appendix 9.4.1

Exclusion Criteria

1. Exhibited any primary generalized seizures (e.g., absence, myoclonic, primary generalized tonic-clonic seizures).
2. Had status epilepticus within the 24 weeks prior to, or during, the Baseline Phase.
3. Was taking an EIAED (e.g., carbamazepine, phenytoin, phenobarbital, primidone) or was taking more than 1 background AED.
4. Was currently taking lamotrigine or had previously had an adequate trial of lamotrigine.
5. Was currently taking felbamate.
6. Was using hormone therapy.
7. Was abusing alcohol and/or other substance(s).
8. Had taken an investigational drug within the previous 30 days or planned to take an investigational drug anytime during the study.

9. Was receiving chronic treatment with any medication that could have influenced seizure control.
NOTE: Use of benzodiazepines was allowed as rescue medication, limited to 2 acute uses during each of the baseline, conversion and monotherapy phases.
10. Was currently following the ketogenic diet.
11. Was using vagal nerve stimulation
12. Was planning surgery to control seizures during the study.
13. Was pregnant, breastfeeding, or planning to become pregnant during the study or within the 3 weeks after the last dose of study drug.
14. Was suffering from acute or progressive neurological disease, severe psychiatric disease, or severe mental abnormality that was likely to interfere with the objectives of the study.
15. Had any clinically significant cardiac, renal, hepatic condition, or a condition that affected the absorption, distribution, metabolism or excretion of drugs.

6.1.2 Demographics

Table 2 LAM30055 Study Demographics

Demographic Characteristic	LTG XR 300mg/day N=112	LTG XR 250mg/day N=111
Age (years)		
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Age Group (years), n (%)		
<16	10 (9)	7 (6)
16-65	100 (89)	104 (94)
>65	2 (2)	0
Gender, n (%)		
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
Ethnicity, n (%)		
Hispanic/Latino	33 (29)	30 (27)
Not Hispanic/Latino	79 (71)	81 (73)
Race, n (%)		
African American/African Heritage	5 (4)	4 (4)
Asian - East Asian Heritage	11 (10)	11 (10)
White - Arabic/North African Heritage	0	2 (2)
White – White/Caucasian/European Heritage	96 (86)	94 (85)
National Origin		
US	28 (25%)	28 (25%)

Ukraine	33 (29%)	27 (24%)
Russia	15 (13%)	20 (18%)
Argentina	14 (12%)	13 (12%)
Korea	11 (10%)	11 (10%)
Costa Rica	7 (6%)	9 (8%)
Chile	5 (4%)	5 (4%)

Demographic characteristics were comparable between the treatment groups with the exception of fewer females in the LTG XR 300mg/day group (50%) relative to the LTG XR 250mg/day group (59%). Mean age was 33.8 and 32.9 years, respectively, and the majority of subjects in both treatment groups were 16 to 65 years, not Hispanic/Latino, and of White – White/Caucasian/European Heritage, table 2.

National Origin: A total of 226 subjects (n = 113 per treatment group) were randomized from 7 countries. The majority of these subjects were randomized in the Ukraine (29% [LTG XR 300mg/day] and 24% [LTG XR 250mg/day]), the US (25% for both groups), and the Russian Federation (13% and 18%, respectively). The remaining subjects were randomized in Argentina (12% for both groups), Korea (10% for both groups), Costa Rica (6% and 8%, respectively), and Chile (4% for both groups), table 2 above. Finally, subjects were randomized at a total of 57 sites with no single site randomizing more than 7% of all subjects..

6.1.3 Subject Disposition

Table 3 LAM30055 Subject Disposition

	LTG XR 300mg/dayN =113	**LTG XR 250mg/dayN =113**
Completion status, n (%)		
Completed study[1]	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Reason for premature withdrawal, n (%)		
Adverse event (AE)	4 (4)	10 (9)
Lost to follow-Up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response	6 (5)	7 (6)
Other, specify[2]	0	1 (<1)
1. A subject was considered to have completed the study if (s)he completed the Baseline, Conversion and Monotherapy Phases of the study. 2. Other, specify = Subject 130 withdrew due to pregnancy		

Fewer subjects were prematurely withdrawn from the LTG XR 300mg/day group (17%) relative to the LTG XR 250mg/day group (30%). This difference was due to fewer subjects in the 300mg/day group who were discontinued due to AE(s), lost to follow-up, and discontinued with protocol violations. The most common reason for withdrawal from the 300mg/day group was “subject decided to withdraw from the study” (8%). For the 250mg/day group, AE was the most frequent cause for withdrawal (9%).

Study 30/31

Introduction

Study 30/31 was the pivotal trial for approval of Lamictal IR for conversion to monotherapy in patients with partial seizures. This study represents two studies, 30 and 31 which were combined due to slow enrollment. They were combined prior to breaking the blind in order to ob tin one study with the required sample size. These studies were of identical design. The primary objective of the study was to compare the efficacy and safety of Lamictal monotherapy 500mg/day to valproate monotherapy 1000mg/day in adult outpatients. Efficacy was based on the proportion of patients who discontinued treatment due to meeting escape criteria. Study 30/31 was also study number 2 of the White Paper Table 1) whose valproate treatment arm contributed to the aggregate pseudoplacebo group of the White Paper.

Study 30/31 is included as a supportive efficacy study in this sNDA. The design of study 30/31 was similar to study LAM3005. A full description of study 30/31 may be seen in the review of efficacy p43.

6 Review of Efficacy

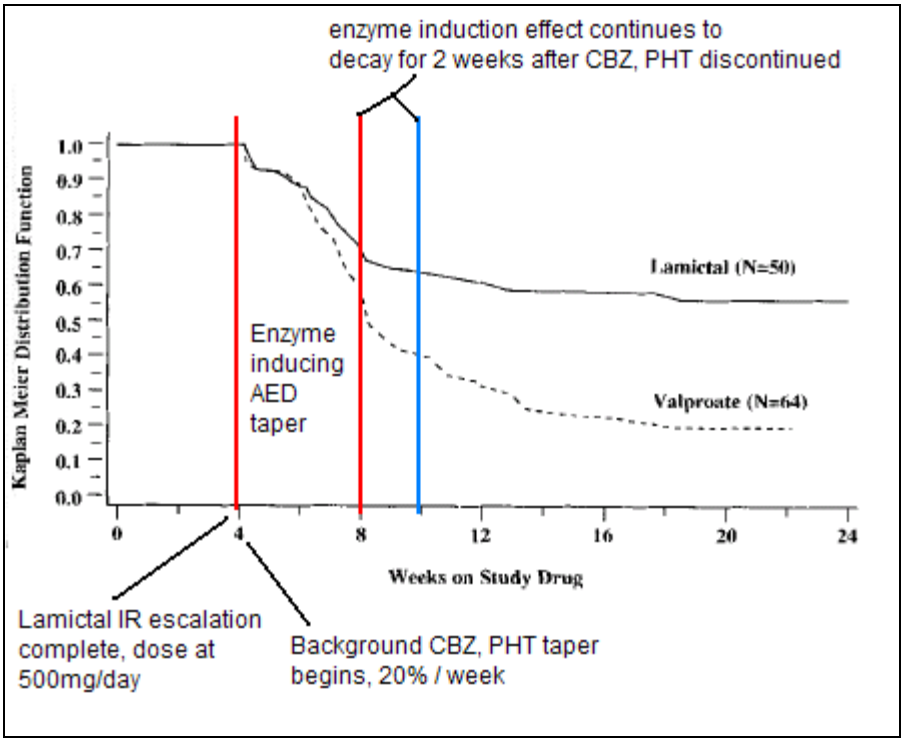
6.1 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has requested an indication for 250mg/day to 300mg/day for use in conversion to monotherapy at a dose of 250mg/day to 300mg/day in patients ≥ 13 year of age with partial seizures who are receiving treatment with a single AED. There is some contrast between this dose and the approved dose of LAMICTAL IR for conversion to monotherapy which is 500mg/day. In addition the approved dose for LAMICTAL IR as adjunctive therapy for patients on enzyme induction neutral AEDs is 300mg/day to 400mg/day.

The sponsor supports this lower target therapeutic range with the results of study LAM30055 discussed in section 6.1, the combined statistical & Clinical Review of Efficacy. The historical control design of this study was accepted unanimously by an advisory committee meeting (section 9.3). The results of of the study were accepted as substantial evidence of effectiveness for Lamictal XR as monotherapy were also accepted by the committee.

The sponsor indicates the choice of Lamictal XR dose in study LAM30055 is supported by the observation that a separation was seen between Lamictal IR and patients on pseudoplacebo (VPA 1000mg/day), between weeks 4 and 10, during and following the conversion interval from enzyme inducing AEDs (carbamazepine & phenytoin). During this interval, although the patient is on 500mg /day of Lamictal IR, the effective dose is approximately 250mg due to the 2 fold increase in metabolism of lamotrigine caused by enzyme induction (figure 4). Addition support for the dose of 250mg/day and 300mg/day in study LAM30055 is provided by a double blind study of lamotrigine monotherapy 150mg/day compared to carbamazepine 600mg/day. In this study In addition lamotrigine IR at a median dose of 150mg has demonstrated effectiveness similar to carbamazepine in an active comparator study[4].

Figure 4 Kaplan-Meier distribution curve of time to escape showing separation of Lamictal IR from Pseudoplacebo during interval of depressed lamotrigine levels due to effect of enzyme induction[5]



Reviewer Comment: The choice of Lamictal XR dose for study LAM30055 is lower than Lamictal IR monotherapy based on pharmacokinetic observations of the

4 Bodie MJ, Richens A, Yuen AWC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. The Lancet 1995;345:476-479.
5. Gilliam F, Vasquez B, et al. An active-control trial of lamotrigine monotherapy for partial seizures. Neurology1998;51:1018-1025.

conversion phase of study 30/31 and an active comparator trial of lamotrigine and carbamazepine in newly diagnosed seizures. This choice was supported by the outcome of study LAM30055 as discussed in section 6.1 and 9.3.

6.1 Combined Statistical & Clinical Review of Efficacy

6.1.1 Executive Summary

Statistical Reviewer Summary

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study (Study LAM30055) evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control from the White Paper (see French et al, Epilepsia 20106 for the published version of the White Paper). The use of historical control for monotherapy was mainly due to ethical and clinical consideration. However, due to lack of internal control, Study LAM30055 suffered from the common problems that usually arose in historical controlled trials, such as potential bias, non-comparability of treatment groups to the historical control, and difficulty in interpreting efficacy results.

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

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

To make an attempt to adjust for biases, the reviewer conducted analyses which
(1) calculated escapes according to more stringent Escape Criteria used in some of the White Paper studies

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

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

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

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

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

Clinical Reviewer Summary

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

To use an historical control method a study is required to have design features which allow comparability between a current study and the historical control studies. Key criteria are similarity of study design, population, evaluation criteria and analysis plan. Study LAM30055 met this requirement in the elements of conversion to monotherapy, study endpoint and analysis plan; however there was notable divergence in the study population. The first point of divergence was in the composition of the historical control population which was approximately 100% of US patients while LAM30055 was only 25% US. The second divergence was in the allowed number of background AEDs prior to monotherapy conversion. Six of the 8 historical control studies allowed 2 baseline AEDs whereas LAM30055 allowed only one AED for eligibility. In addition to these disparities a difference in study endpoint profile emerged. In the calculation of the White Paper prediction interval and the Lamictal XR monotherapy endpoint confidence interval

both were based on percent of patients meeting any of 4 escape criteria; however the Lamictal Study had no criteria # 4 escapes where the historical control studies had escapes due to criteria # 4 ranging from 4% to 45%. In addition the Lamictal XR monotherapy study had lower rates of escape reporting across all criteria.

The statistical reviewer identifies the sources of bias which include different methods of calculating escapes between the Lamictal XR study and the White Paper studies, treatment of dropouts, medical (1 or 2 background AEDs) and regional differences in the study population and under reporting of escapes, especially problematic in Criteria 4. The statistical approach to compensate for the bias was to perform a recalculation of escapes using more stringent criteria which included dropouts as treatment failures and reanalyzed the historical control (White Paper) dataset using only those patients on a single background AED. There was no clear approach to compensate for the divergence in escape criteria # 4 between the Lamictal XR study and the White Paper studies.

A recalculation of the White Paper prediction interval lower bound based on the population taking only 1 AED yielded a value of 58.6%. Both the 300mg/day and 250mg/day dose groups of the Lamictal XR monotherapy study retain superiority to this threshold in all adjustments to the White Paper escapes (table 12). The US subset of the Lamictal XR monotherapy study retains superiority only in the least conservative White Paper per protocol analysis (table 13).

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

Clinical Reviewer Conclusion

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

6.1.2 Introduction

Overview

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

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

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

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

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

Clinical Reviewer Comment

History of Lamictal and Lamictal XR Pertaining To the Current Application

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

A clinical pharmacology review was performed for the submission of Lamictal XR for adjunctive therapy of partial seizures[7]. In the evaluation of proposed conversion dose from lamotrigine IR to Lamictal XR the reviewed examined the lamotrigine steady state relative bioavailability in 3 groups of patients receiving different concomitant AEDs (enzyme inducers, inhibitors and neutrals). The reviewer found the following:

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

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

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

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

Table 4 Bioavailability of LAMICTAL XR and LAMICTAL IR

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

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

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

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

There is a robust history of Lamictal XR use, as shown in the table below representing the interval from May 29, 2009 to July 24, 2010. There were (b) (4) mg (the equivalent of (b) (4) 200mg tablets) of Lamictal XR sold in the US in this interval, not including start up kits, freely provided drug or samples[8].

Table 5 Lamictal XR distribution data

DISTRIBUTION DATA NDA 022-115; LAMICTAL XR EXTENDED-RELEASE TABLETS May 29, 2009 to July 24, 2010				
Description	**NDC Code**	**Domestic Sales**	**Domestic Free Issues**	**Domestic Samples**
LAMICTAL XR TABLETS 25MG 30s	0173075400	(b) (4)		
LAMICTAL XR TABLETS 50MG 30s	0173075500			

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LAMICTAL XR TABLETS 100MG 30s	0173075600	(b) (4)
LAMICTAL XR TABLETS 200MG 30s	0173075700	
LAMICTAL XR TABLETS 25MG/50MG STARTER KT	0173075800	
LAMICTAL XR TAB BLUE DE KIT 25MG/50MGSPL	0173075860	
LAMICTAL XR TABLETS 50MG/100MG/200MG KIT	0173075900	
LAMICTAL XR TAB GREEN DE KIT 50/100/200	0173075960	
LAMICTAL XR TABLETS 25MG/50MG/100MG KIT	0173076000	
LAMICTAL XR TAB ORANGE DE KIT 25/50/100	0173076060	

Data Sources

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

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

6.1.3 Statistical Evaluation

Evaluation of Efficacy

Study LAM30055

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

Study Design (see 5.3)

This was an international, multicenter, double-blind, randomized study of 2 doses (300 and 250 mg/day) of lamotrigine extended-release (LTG XR) tablets comparing the

premature discontinuation rate for each dose to an historical escape rate (65.3%) determined from aggregated pseudo-placebo data. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy dose of LTG XR than the currently approved 500 mg/day of LTG IR.

The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy. Subjects who completed the Treatment phase or met Escape Criteria were allowed to enter the Continuation phase. Study phase and duration was shown in Table 6. Approximately 230 male or female ≥13 years of age with partial epilepsy with seizures uncontrolled (>=2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio.

Table 6. Study Design

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

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

Efficacy Measures

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

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

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

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

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

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

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

Statistical Analysis Methods

Analysis Population

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

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

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

Efficacy Analyses

The planned primary treatment comparison in study LAM30055 evaluated the proportion of subjects who discontinued LTG at 300 mg/d during the last 16 weeks of treatment with LTG XR compared to an historical pseudo-placebo control rate. This pre-specified primary endpoint of ‘all-cause’ discontinuation was based on the way Study US 30/31 data was analyzed as part of the aggregation of 8 studies included in the

historical database. After completion of the double-blind phase of LAM30055, it was learned that the analysis of US 30/31 in the 2005 version of the White Paper was incorrect. US 30/31 data were subsequently re-analyzed utilizing only escape data. In response to this, data from LAM30055 were analyzed post-hoc focusing only on subjects who met Escape Criteria. Since this was the endpoint used in the White Paper, the Escape Criteria analyses was referred as post-hoc primary analysis.

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

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

Patient Disposition, Demographic and Baseline Characteristics

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

Table 7 Subject Disposition

	Number (%) of Subjects	
	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Population		
Randomized	113	113
Safety	112 (>99)	111 (98)
Intent-to-Treat (ITT)	112 (>99)	111 (98)
Per Protocol (PP)	93 (82)	81 (72)
White Paper PP	108 (96)	97 (86)
Subject Disposition (Randomized Subjects)		

	Number (%) of Subjects	
	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Completed study	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Met Escape Criteria[1]	28/112 (25)	25/111 (23)
Reason for premature withdrawal		
Adverse event	4 (4)	10 (9)
Lost to follow-up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response[2]	6 (5)	7 (6)
Other, specify[3]	0	1 (<1)

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

Source: Sponsor ISE page 23.

The majority of subjects in both treatment groups were 16 to 65 years and of White – White/Caucasian/European heritage (Table 8).

Table 8 Study LAM30055 Demographics

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

Source: Sponsor ISE page 26.

Most subjects in both treatment groups had only partial seizures at Baseline. The median Baseline seizure frequency (number of partial seizures/week) over the entire Baseline was 1.4 for the LTG XR 300 mg/day group and 1.5 for LTG XR 250 mg/day group. Seizure history at Baseline was similar for the two treatment groups with a mean age of 20.5 and 18.7 years, respectively at first seizure, and a mean of 14.3 and 15.2 years, respectively for duration of epilepsy (**Error! Reference source not found.**.)

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

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

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

Source: Sponsor ISE page 27.

Sponsor's Efficacy Results

Planned Analyses Results

Primary efficacy endpoint

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

Secondary efficacy endpoints

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

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

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

Table 9. Summary of Planned Analyses (PP population)

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

	LTG XR 300 mg/day N=93	LTG XR 250 mg/day N=81
Entire Treatment Period, n	93	81
≥50% reduction, n (%)	54 (58.1)	42 (51.9)
Seizure-free (100% reduction), n (%)	3 (3.2)	4 (4.9)

1. Positive number means a decrease in seizure frequency
2. Paired t-test

Source: Sponsor ISE Table 5 & 6.

Post-hoc Analyses Results

The post-hoc primary analysis was the percent of subject meeting Escape Criteria in the White Paper population. While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, the analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small: only 6 to 7 subjects in each group were discontinued due to meeting Escape Criteria (Table 10).

Post-hoc evaluation of the seizure data led to reclassification of many subjects as escapes (i.e., having met Escape Criteria) (Table 10). The proportion of subjects who met calculated Escape Criteria was 24% for the LTG XR 300 mg/day group and 26% for the LTG XR 250 mg/day group. The upper 95% confidence limit did not overlap the lower 95% prediction limit (65.3%) from the historical pseudo-placebo control data for both groups.

Table 10. Proportion of Subjects Meeting Escape Criteria (Sponsor Results for White Paper PP Population)

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

Source: Sponsor ISE Table 2, 8, 11.

Reviewer's Results

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

Evaluation of the Escape Criteria

Escape Criterion #1: doubling of average monthly seizure frequency

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

In Study LAM30055, the sponsor calculated the average monthly seizure frequency as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. As calculating the highest seizure frequency for *any* consecutive 28 days was more stringent and was used for some of the White Paper studies, the reviewer used this method for Study LAM30055. Three additional subjects in each group were identified to have met this Escape Criterion, resulting in 3 more escapes for the LTG XR 300 mg/day group and 2 more escapes for the LTG XR 250 mg/day group (one subject in the 250 mg/day group met multiple Escape Criteria).

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

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

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

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

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

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

The data suggested that none of the subjects met this criterion (Table 11). The escapes based on this criterion were solely evaluated by the sites/investigators. The sponsor did not perform the re-calculation due to the subjective nature of this criterion. It was recognized the investigators tended to under-report escapes for criteria 1, 2 and 3. Therefore, there was concern that the escapes due to this criterion were also under-reported.

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

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

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

Table 11. Percentage of Subjects Meeting Each Criterion

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

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

Statistical Analysis of the Proportion of Subjects Meeting Escape Criteria

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

estimated binomial proportion will be smaller than the Kaplan-Meier estimate due to the different ways of handling dropouts.

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

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

None of the upper 95% confidence limits generated by all of these analyses are greater than the White Paper 95% prediction limit for escapes (65.3%) from the historical pseudo-placebo control data (Table 12).

Table 12. Proportion of Subjects Meeting Escape Criteria

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP		
n/N (%)	31/108 (29)	30/97 (31)
[95% CI]	[20.2, 37.2]	[21.7, 40.1]
White Paper PP Sensitivity Analysis		
n/N (%)	37/108 (34)	37/97 (38)
[95% CI]	[25.3, 43.2]	[28.5, 47.8]
ITT Worst Case Analysis		
n/N (%)	41/112 (37)	51/111 (46)
[95% CI]	[27.7, 45.5]	[36.7, 55.2]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

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

Clinical Reviewer Comment

Study LAM30055 had no escapes due to category #4. This raises a concern of under reporting of escapes. One escape was identified in the adverse event dataset which fits the more general category 4 of the white paper. The observation of no criteria 4 escapes prompts a closer examination of the parity of escape criteria between study LAM30055 and the White Paper composite criteria. The individual criteria are captured for each study and shown in appendix 1. The White Paper creates a composite criteria 3 and 4 which acceptably captures criteria 3 and 4 of the 8 White Paper studies;

however as can be seen in the "matching" column of the table (appendix 1), 5 of 7 studies where the data is available do not have strict 1:1 matching with the criteria of LAM30055. Criteria 1 and 2 best approximate a clear 1:1 mapping between the Lamictal XR monotherapy study and the White Paper studies but the distinction is blurred for criteria numbers 3 and 4 which confounds a clear statistical solution to this bias.

Evaluation of the Study Population

Background AED

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

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

Clinical Reviewer Comment

The LAM30055 design allowed patients only on stable monotherapy to enter the trial. As noted above, this design is divergent from White Paper studies which allowed up to two background AEDs. There is a potential for the population on stable monotherapy to be less refractory than those requiring polytherapy. Those on two AEDs may be more prone to escape events. The statistical reviewer has reanalyzed the White Paper dataset with modifications which restricted analysis to patients on one background AED. When compared to the revised 58.6% lower bound prediction interval the upper 95% CI of both the 300mg/day and 250mg/day dose groups of study LAM30055 remain superior to the pseudoplacebo group (table 12).

Regional Comparisons

Study LAM30055 was conducted in 7 countries (Argentina, Chile, Costa Rica, Korea, Russian, Ukraine and US) with approximately 75% of subjects enrolled outside the US. In contrast, virtually all of the subjects in the historical control database were enrolled in the US. Table 13 showed the percent escape by region (US vs non-US). Due to the small size in the US, the two dose groups (300 mg/d and 250 mg/d) were pooled. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The proportion of US subjects meeting Escape Criteria remained superior to the historical control except for the ITT worst case analysis. When comparing to the

prediction limit for subgroup of patients with one background AED, LTG XR did not show superiority over the historical pseudo-placebo for the US population in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 13).

Table 13. Proportion of Subjects Meeting Escape Criteria by Region

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

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

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

The above argument was not convincing in the reviewer's opinion. As shown in Table 14, the escape rates were similar between VPA and neutral AEDs within each region. The escape rate was higher at US compared to non-US sites for each type of background AEDs.

Table 14. Region and Background AED Comparisons (White Paper PP)

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

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

The Agency requested the Sponsor to establish the comparability of placebo escape rate among the regions. The Sponsor provided US vs non-US placebo rates for recent

LAMICTAL adjunctive studies, and conducted literature review of analysis of placebo response by region for various indications. While there may be regional differences in placebo response, the data was limited and the regional differences were inconsistent (sometimes higher in the US, sometimes non-US).

Clinical Reviewer Comment

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

The concern of generalizability to the US population is addressed first. There is uncertainty about the comparability of US to foreign clinical trial sites, especially those that are non-North American, non-Western European sites. There may be differences between the US and foreign sites based on differences in practice of medicine, cultural framework of heath care, the level of investigator and staff training at non-US sites and pharmacogenomic differences in the studied population[9].

There is a suggestion of differences between US and Non-US populations in prior Lamictal XR trials. In study LAM0034 a placebo controlled trial of Lamictal XR for treatment of partial seizures, which was composed of approximately 40% US sites, the efficacy subset analysis of US sites did not reach a threshold of significance. This raised a concern that efficacy within the study as a whole was driven by the foreign data. In study LAM00036, a placebo controlled trial of Lamictal XR in primary generalized tonic-clonic seizures; the placebo response of the US sites was notably larger than in the non-US sites. In another placebo controlled study (LAM40097) of Lamictal XR in primarily generalized tonic-clonic seizures the findings were reversed with a placebo response in the non-US sites which was larger than the US placebo response rate. The reversal in placebo response rate between studies LAM0036 and LAM40097 suggests non-systematic variation in the placebo response between studies, a favorable observation, which at face value poses less of a challenge to the generalizability of foreign data to the US. The situation may be more complex. In study LAM40097 the non-US placebo treatment patients were all from South America whereas in study LAM0036 only 16% of 62 non-US, placebo treated patients were from South America and the remainder were from Germany, Russia, Ukraine, Malaysia, and India. The majority were from India. Therefore it may be postulated that there is a higher placebo response in the South American cohort which was diluted, in this second case, by the larger numbers of European and Asian patients. In conclusion, regional differences in placebo response cannot be ruled out by the reversal of placebo response observations in studies LAM100036 and LAM40097.

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

In the current study, LAM0035, there is a divergence in the escape rate between the US and non-US patient groups. The upper 95% CI of the US subset was below the original White Paper lower CI of the prediction interval (65.3%) for the White Paper PP analysis and the White Paper sensitivity analysis (table 13), Subsequently following a reanalysis of the White Paper with only patients on one background AED included, the statistical reviewer has found the US subset breaches the resulting modified White Paper lower bound of 58.6% in both the ITT worst case analysis and the White Paper sensitivity analysis (table 13). This observation is again suggestive of a different population behavior in the US and non-US cohorts.

The sponsor analysis explained this difference as, quite plausibly, due to imbalance in treatment with valproic acid (VPA) as a background anticonvulsant agent. In order to further investigate this possibility the statistical reviewer has performed an analysis of the LAM30055 escape rate by background AED type, either VPA or enzyme induction neutral. The US and non-US escape rates were extracted. This analysis revealed that within region the background AED is not associated with a difference in escape rate (table 14). This observation undermines the proposition that difference in the proportion of patients entering the study with VPA as a background AED is responsible for the difference in US vs non-US escape rate. The cause of this difference remains unexplained but underscores the concern that non-US cohorts may not be generalized to the US population.

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

Baseline Seizure Frequency

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

Table 15 showed that the escape rate was 42% for subjects with Baseline seizure frequency less than 4 per 4 weeks and 25% for subjects with Baseline seizure frequency of at least 4. The escape rate was higher for the subset of patients with 2-4 seizures per 4 weeks at Baseline. Therefore, there was no evidence that the relatively low Baseline seizure frequency in Study LAM30055 led to lower escape rate.

Table 15. Escape Rate by Baseline Seizure Frequency (White Paper PP)

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

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

Clinical Reviewer Comment

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

Baseline Seizure Types

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

Table 16 showed that the escape rate was higher for the subset of patients without CP in Study LAM30055. Therefore, there was no evidence that the lower percentage of subjects with CP in Study LAM30055 contributed to the lower escape rate.

Table 16. Escape Rate by Baseline seizure Type (White Paper PP)

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

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

Clinical Reviewer Comment

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

Supportive Study (LTG IR) – US 30/31

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

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

Subject disposition was presented in Table 17. A total of 156 subjects were randomized. The ITT Population which consisted subjects randomized to treatment who received at least one dose of the assigned treatment included 76 subjects in the LTG IR group and 80 subjects in the VPA group. The PP Population of subjects who met Escape Criteria or completed 12 weeks of monotherapy (i.e., completers; differently from Study LAM30055 PP) included 50 subjects in the LTG IR group and 64 subjects in the VPA group. More subjects in the LTG IR group than the VPA group prematurely discontinued the study (34% vs 20%, respectively) for reasons other than having met Escape Criteria, primarily due to a higher occurrence of AEs (20% vs 8%, respectively).

Table 17. Subject Disposition (All Randomized Subjects: Study US 30/31)

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

Source: Sponsor ISE Table 16.

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

significant difference between LTG and VPA. Other analyses showed that LTG was superior (Table 18).

Table 18. Proportion of Subjects Meeting Escape Criteria (Study US 30/31)

	Number n/N (%) of Subjects	
	LTG IR	**VPA**
US 30/31 PP Population[1]	22/50 (44)	51/64 (80)
ITT	48/76 (63)	67/80 (84)
ITT worst case analysis	48/76 (63)	51/80 (64)
ITT Agency[2]	32/76 (42)	55/80 (69)

1. Different from the PP population is Study LAM30055.
2. Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to AEs were not counted as escapes.

Source: Sponsor ISE Table 19-21.

6.1.4 Findings in Special/Subgroup Populations

Gender, Race and Age

Table 19 showed the subgroup analysis results for age, gender and race subgroups for Study LAM30055. Majority of the patients are 16 years old or older (92%), White (87%), female (53%). The escape rate was consistent across the race subgroups, but appeared higher in young (<16 years) and old (>=55 years) male patients. Logistic regressions indicated that there was no effect of age or gender on the escape rate.

Table 19. Escape Rate by Gender, Race and Age in Pooled Treatment Group (Study LAM30055 White Paper PP)

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

Source: FDA reviewer.

6.1.5Summary and Conclusions

Statistical Issues and Collective Evidence

The formulation and dosage of LTG were different in the pivotal study LAM30055 and the supportive study US 30/31. The main differences in study design between the two studies were (1) Study US 30/31 was placebo-controlled but Study LAM30055 was not; (2) Study US 30/31 was conducted in the US while Study LAM30055 was conducted in 7 countries with approximately 75% of subjects enrolled outside the US; (3) and Study US 30/31 included only subjects taking an EIAED as their background monotherapy but Study LAM30055 excluded subjects taking EIAEDs. The study results were presented in Table 20. The proportion of subjects meeting Escape Criteria was lower in Study LAM30055 than Study US 30/31. The identified issues were discussed below.

Table 20. Summary of Escape Rate by Study

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

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

Post-hoc Analyses

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

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

While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, planned analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small. Only about 6% of the subjects met Escape Criteria compared to 42% in Study US 30/31 (Table 21). Therefore, to correct errors by sites/investigators, seizure data were evaluated post-hoc leading to reclassification of many subjects as 'escapes' (Table 20).

Table 21. Escapes As Determined by Investigator (ITT Population)

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

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

Potential Biases

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

In Study LAM30055 subjects who dropped out for reasons other than meeting Escape Criteria were treated as completers in the sponsor's analysis, which biased toward treatment success (analysis for White Paper PP population). The White Paper used Kaplan-Meier estimate of the proportion, in which subjects dropped out due to other reasons were censored. This gives a higher estimated escape rate. The reviewer conducted a sensitivity analysis which included dropouts as treatment failures. This was also the planned primary endpoint of 'all-cause' discontinuation. To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes. The results remained positive for those analyses (Table 20).

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

Population Comparability

Study LAM30055 had approximately 75% of subjects enrolled outside the US while all of the subjects in the historical control database were enrolled in the US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The comparability of the US and non-US subjects was not established. The result for the US subgroup was positive except for the ITT worst case analysis (Table 13).

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. In comparison to this limit, both LTG dose groups remained superior to the historical pseudo-placebo. However, LTG XR failed to show superiority for the US subgroup in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 13).

Conclusions and Recommendations

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

Clinical Reviewer Comments

The sponsor analysis revealed an unexpectedly low escape rate prompting re-evaluation of seizure data to create “calculated escapes”. The proportion of subjects meeting escape criteria based on this analysis was 26/108 (24%) with lower and upper bound of 95% confidence intervals of 16% and 32.1% respectively for the 300mg /day

group. The statistical reviewer notes that the sponsor analysis conducted for the White Paper per protocol population is based on the binomial proportion of subjects meeting escape criteria. The reviewer indicates that the White Paper used Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored. This results in a larger estimate of escapes. The statistical reviewer also created two additional analysis of the proportion of subjects meeting escape criteria, these three analysis methods are defined for as follows:

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

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

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

The results of study LAM30055 based on these analysis may be seen intable 12. Based on the White Paper 95% prediction limit of 65.3% all of the 300mg/day or 250mg/day upper 95% confidence intervals in addition to the US subset where the White Paper per protocol and sensitivity analysis remain superior to this threshold (table 13).

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

In 6 the 8 White Paper studies where the data is available the participants were on 2 background AEDs at entry while study LAM30055 required background monotherapy for eligibility. The statistical reviewer has found that the White Paper data indicate that patients with one background AED had fewer escapes than patients with two AEDs. An analysis of the White Paper pseudoplacebo population on only 1 background AED is performed and reveals a Kaplan Meier escape rate of 83% with a lower bound prediction interval of 58.6%. The overall study LAM30055 results were not changed based on the statistical reviewer escape groups oftable 12. The US subset results did lose superiority to the White Paper sensitivity analysis (table 13)

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

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

The use of an historical control comparator is a novel methodology. There are multiple components of the White Paper pseudoplacebo aggregate which present a challenge to confidence in this approach as a valid comparator to study LAM30055. The populations are different across time and region. The span of the pseudoplacebo population ranges from approximately 1992 to 2001. In the oldest White Paper study the pseudoplacebo patients will be almost a generation older than the study population of LAM30055. The regional divergence is discussed above. The variation in mapping of escape criteria between the Lamictal XR monotherapy study and the White Paper studies are features which point to insufficient uniformity between studies to act as a pooled comparator. There are also features which support the validity of this aggregate pseudoplacebo group. First, in every study the pseudoplacebo escape rate was larger than the active therapy escape rate and in 6 of 7 studies where the data is available; the active therapy was statistically superior to the pseudoplacebo arm (see appendix 2). The common core feature of all 8 White Paper trials was a study endpoint of patient exit (escape) rate.

Additional support for efficacy is provided by the bioequivalence data on Lamictal IR and XR presented in the Clinical Pharmacology review of Lamictal XR (adjunctive therapy in partial seizures)10. This data provides an expectation that this extended release form of Lamictal will perform similarly to Lamictal IR which is approved for conversion to monotherapy. Conceptual support for efficacy of Lamictal XR monotherapy is provided by the established effectiveness of Lamictal XR for treatment of partial and primary generalized tonic-clinic seizures.

Summary

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

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

Conclusion

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

7 Review of Safety

Safety Summary

From Protocol LAM30055

Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE **include**:

• Significant or unexpected worsening or exacerbation of the condition/indication under study. See Section 10.3, “Lack of Efficacy”, for additional information.
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
• Significant failure of expected pharmacological or biological action. See Section 10.2.1, “Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs” for additional information.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety grouping for the sNDA is comprised of the subjects in the double blind phase of study LAM30055, also the principle efficacy study.

An additional panel of studies provides supportive safety information. This panel includes an open label phase of study LAM30055 as well as clinical studies conducted with lamotrigine IR. The lamotrigine IR studies include five controlled and four uncontrolled studies and are collectively referred to as “Completed Monotherapy Studies”

The five controlled, lamotrigine IR monotherapy studies include the pivotal monotherapy study (US 30/31), four monotherapy studies in newly diagnosed subjects (UK 49, UK 74, UK 89, and UK 106). The four uncontrolled studies include: one conversion to monotherapy study (UK 105) and three continuation trials (UK115, UK 111, UK 112), table 18, Study Grouping.

Table 22 Study Grouping

Study Grouping	Studies
Principal Efficacy Study	double-blind Treatment Phase of Study LAM30055
Long-term Continuation Data	open-label Continuation Phase of Study LAM30055
Supportive Efficacy Study (LTG IR)	double-blind Treatment Phase of Study US 30/31
Completed Monotherapy Studies (LTG IR)	double-blind Treatment Phase of Study US 30/31 double-blind Treatment Phase of Study UK 49 double-blind Treatment Phase of Study UK 89 double-blind Treatment Phase of Study UK 74 open-label, controlled Treatment Phase of Study UK 106 open, conversion to monotherapy Study UK 105 open Continuation Study UK 115 open Continuation Study UK 111 open Continuation Study UK 112
	(b) (4)

A table of the characteristics of the individual studies contributing to the safety information is provided below (table 23). This table contains a brief description of the type of study for each study number.

Table 23 Study Characteristics and Data Provided

Study Number	Status of Study	Type of Study	Number of Subjects in Safety Population	Information Provided	GSK CSR Document Number
Phase III Studies					
LAM30055 (double-blind Phase)	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 22 to 23 weeks blinded	223	All safety data	RM2008/00412/01
LAM30055 (open-label Phase)	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 24 weeks open-label	195	All safety data	RM2009/00139/01
US 30/31	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 12 weeks blinded, double-blind, compared to VPA	76	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 49/UK 89	Complete	Efficacy and safety, partial seizures and generalized tonic-clonic seizures, LTG monotherapy compared to CBZ	131	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 74	Complete	Efficacy and safety, double-blind, partial seizures with or without secondarily generalized tonic-clonic seizures and primary generalized tonic –clonic seizures, LTG monotherapy compared to PHT	85	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 106	Complete	Efficacy and safety, open-label, partial or generalized tonic-clonic seizures, LTG monotherapy compared to CBZ	230	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 105	Complete	Efficacy and safety, open-label, 16 weeks add on to 1 AED, 12 weeks AED withdrawal, 12 weeks LTG monotherapy	345	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 115	Complete	Safety and efficacy, open-label continuation for subjects who completed UK 49, UK 89 or UK 74.	52 (from UK 49/UK 89 and UK 74)	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 111	Complete	Safety and efficacy, open-label continuation for subjects who completed, or withdrew for a seizure, from UK 106.	67 (from UK 106)	All safety data	NDA 20-241/S003, approved 14 December 1998

UK 112	Complete	Safety and efficacy, open-label continuation for subjects who completed UK 105.	135 (from UK 105)	All safety data	NDA 20-241/S003, approved 14 December 1998
Ongoing Studies (Synopses Only)					
(b) (4)					

7.1.2 Categorization of Adverse Events

In order to capture most accurately the definitions of adverse events in the studies contributing to the safety dataset of this sNDA the following definitions of adverse events are taken directly from the Sponsor's Summary of Clinical Safety.

Definition of an Adverse Event

Study Number	Definition of an AE
LAM30055	An AE was defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a
LEP105972	Medicinal product, whether or not considered related to the medicinal product. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, an AE could also include failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.
Completed Monotherapy Studies: US 30/31, UK 49, UK 89, UK 74, UK 106, UK 105, UK 112, UK 115, UK 111	An AE was any undesirable medical experience/event occurring to a subject during participation in the study, whether or not the experience/event was considered related to the investigational drug.

Definition of a Treatment Emergent Adverse Event
TEAEs in this CSS are defined as any event that increased in intensity from the Baseline Phase or had an initial onset during the Treatment Period. The TEAE definition is consistent with that used for the Completed Monotherapy Studies (LTG IR).

Definition of Serious adverse events:

In studies LAM30055 and LEP105972 an SAE was defined as any untoward medical occurrence that at any dose: Resulted in death

- Was life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Required hospitalization or prolongation of existing hospitalization

  NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE was considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

- Resulted in disability/incapacity

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Was a congenital anomaly/birth defect

Study US 30/31 and in the Completed Monotherapy Studies-

an SAE was defined as any AE that suggested a significant hazard, contraindication, side effect, or precaution. This included, but was not limited to, any experience that was fatal, life-threatening, permanently disabling, or required or prolonged inpatient hospitalization. Malignancy, overdose of the study drug, or congenital anomaly (in offspring) were also reported as SAEs. Note that these studies were conducted prior to the change in definition of an SAE.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In this novel application the primary objective was to demonstrate in a single study, the efficacy of lamotrigine extended-release (LTG XR) at 300mg/day compared to pooled historic pseudoplacebo data. There is no group of phase II/III studies with placebo

control for pooling. The completed Monotherapy study group is a pooled data group; however the pooling only provides total adverse events for the lamotrigine IR treatment group. There is no contrast to the active comparator provided. Each of the studies had a different active comparator.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Lamictal XR exposure in controlled and open label monotherapy trials does not meet the guidelines in ICH E1A, however there is extensive experience with the use of Lamictal XR approved and marketed for adjunctive therapy in partial and primary generalized tonic clonic seizures.

In monotherapy trials of Lamictal XR there have been only 2 patients exposed for 1 year at the time of submission and 184 patients exposed for 6 months. There were 177 patients exposed for 32 weeks.

Exposure to Lamictal XR in clinical trials as adjunctive therapy was more extensive and fulfilled the ICH E1A guidelines for exposure to assess clinical safety. In the “All Clinical Studies Grouping” 662 subjects were treated. A total of 558 subjects were exposed to lamotrigine XR for 24 weeks, and 270 subjects for 52 weeks. The safety data package for NDA 22509 provides this data. This submission included the studies of Lamictal XR in partial seizures, primarily generalized tonic clonic seizures and monotherapy, LAM100034, LAM100036 and LAM30055 respectively.

Dose

LAM30055: the Lamictal XR dose in this study was equally divided on randomization between 300mg/day and 250mg/day, 83% and 70% of patients in these dose groups completed the double blind treatment phase respectively.

LAM100036 & LAM100034: The Maintenance Lamictal target dose in these studies were 200mg/day for patients on concomitant VPA, 500mg/day for patients on enzyme inducing AEDs and 300mg/day for patients taking AEDs other than VPA or enzyme inducing anticonvulsant medications.

Demographics

In study LAM30055 mean age is very close in the 250mg/day and 300mg/day groups and are found to be 32.9 years and 33.8 years respectively. In the 300mg dose group sex is divided equally with 50% male and female. In the 250mg dose group there were 59% females and 45% females. Racial distribution is largely caucasian/European in both the 250mg and 300mg dose group at 85% and 86% respectively. There were 4% African American in both groups and 10% east Asian heritage in both treatment groups, table 24.

Table 24 LAM30055 Demographic Characteristics

	LAM30055	
Demographic Characteristic	**LTG XR 300 mg/day N=112**	**LTG XR 250 mg/day N=111**
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
African American/African Heritage	5 (4)	4 (4)
Black	NA	NA
Asian - East Asian Heritage	11 (10)	11 (10)
Asian (Indian)	NA	NA
Asian (Oriental)	NA	NA
White - Arabic/North African Heritage	0	2 (2)
White – White/Caucasian/European Heritage	96 (86)	94 (85)
White	NA	NA
Other	NA	NA

7.2.2 Explorations for Dose Response

Common Adverse events by study dose: The most common adverse events, occurring in at least 5% of patients were more frequent in the 250mg than the 300mg dose group. In the any adverse event category 53% of the 300mg / day group experienced an adverse event and 61% of the 250mg / day group experienced an adverse event. The individual events are shown in table x , section 7.4.1 (common adverse events).

Common adverse events by study phase: In the 300mg/day treatment group 5 of 7 adverse events that reached a frequency threshold of occurrence in greater than 5% of patients, occurred more commonly in the conversion interval of the study and two had a marginal predominance in the monotherapy phase of the study. The five which were more common in conversion were headache, dizziness, Nausea, and rash. Nasopharyngitis and nausea occurred with greater frequency in the monotherapy treatment interval. In the 250mg/ day treatment group 5 of 7 adverse events which a frequency threshold of occurrence in greater than 5% of patients, occurred more

commonly in the conversion interval of the study and two event terms had a marginal predominance in the monotherapy phase of the study. The five occurring more commonly in the conversion interval were dizziness, Nasopharyngitis, nausea, somnolence, and rash. The two adverse event terms more common in monotherapy phase were headache and insomnia, both by only small margins.

Serious adverse events occurred with greater frequency in the lower dose arm of Lamictal treatment. There were 3 (3%) SAEs in the Lamictal XR 300mg/day treatment group compared with 5 (5%) in the Lamictal XR 250mg group. Two of the SAEs in each dose group were related to seizures.

Reviewer Comment: counter to intuition the lower dose Lamictal XR group had a greater occurrence of common adverse events and SAEs (serious adverse events) than the 300mg/day group. Two each of the serious adverse events were related to seizures which is a concern in monotherapy treatment. The timing of these epileptiform adverse events will be explored further in section 7.3.2 (nonfatal Serious Adverse Events)

7.2.3 Special Animal and/or In Vitro Testing

None performed for this submission

7.2.4 Routine Clinical Testing

Routine clinical testing is attenuated in Study LAM30055 due to the extensive prior experience with the active pharmaceutical ingredients. Only a physical examination and full neurologic exam are scheduled at baseline and the end of monotherapy treatment phase, table 21. Clinical laboratory parameters, vital signs, and ECGs, are not monitored during the course of the study as noted in the sponsor statement in the Clinical summary of Safety, see below.

"Clinical laboratory evaluations were not conducted prospectively in Study LAM30055. Because of the extensive database of clinical laboratory data from adjunctive studies with LTG-IR, including the absence of laboratory findings in the previous conversion to monotherapy study with LTG (Study US 30/31), clinical laboratory tests were performed at screening only to confirm eligibility. Additionally, for a drug product that is so well characterized, the absence of a control arm within the study would minimize the interpretability and value of laboratory data." (p 67 CSC)

Table 25 LAM30055 Study Timeline and Activities Schedule

LAM30055		**Screen**	**Baseline**		**Conversion Phase**			**Maintenance Phase**			**Continuation**	**Taper/ Follow-up[1]**
Category	**Event**				**Escalation**		**Withdrawal of Bkg AED**	**Monotherapy**				
	Visit	**V1**	**V2[2]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[3]**	**V10-12**	**V13**
	Week (approximate)	(≤2 weeks)	Base Wk 4	Base Wk 8[4]	Treat Wk 4[4]	Treat Wk 6/74	Treat Wk 10/114	Treat Wk 14/15[4]	Treat Wk 18/19[4]	Treat Wk 22/23[4]	Continuation Wks 4, 12 and 24	
Eligibility	Informed Consent	x										
	I/E Criteria	x										
	Demography	x										
Safety	Medical & Seizure History	x										
	Physical Exam	x								x		
	Urine Pregnancy Test	x										x
	Full Neurological Exam	x								x		
	Hemat/Clinical Chemistry/Urinalysis	x										
	Adverse Events		x[5]	x[5]	x	x	x	x	x	x	x	x
Treatment	Study Drug Dispensing, Accountability and Compliance			x	x	x	x	x	x	x	x[6]	x

LAM30055		**Screen**	**Baseline**		**Conversion Phase**			**Maintenance Phase**			**Continuation**	**Taper/ Follow-up[1]**
Category	**Event**				**Escalation**		**Withdrawal of Bkg AED**	**Monotherapy**				
	Visit	**V1**	**V2[2]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[3]**	**V10-12**	**V13**
	Week (approximate)	(≤2 weeks)	Base Wk 4	Base Wk 8[4]	Treat Wk 4[4]	Treat Wk 6/74	Treat Wk 10/114	Treat Wk 14/15[4]	Treat Wk 18/19[4]	Treat Wk 22/23[4]	Continuation Wks 4, 12 and 24	
	Concurrent AEDs/Compliance and Concurrent Medications	x	x	x	x	x	x	x	x	x	x	x
Efficacy	Seizure Counts		x	x	x	x	x	x	x	x	x	x
Pharmacokinetic	LTG Serum Levels					x[7]		x[7]				
Pharmacogenetic	Blood Sample			x[8]								

1 Assessments 2 weeks after total discontinuation of study medication
2 This visit may be omitted if historic baseline data are used.
3 or premature discontinuation
4 Actual weeks will vary depending on use of historic baseline and background AED
5 SAEs only
6 Additional visits at Continuation Weeks 8 and 16 for dispensing and accountability only
7 Trough sample (Pre-dose)
8 Optional and may be obtained at any visit after Visit 2

Reviewer Comment: due to the extensive background experience with the active pharmaceutical ingredient as noted in 7.2.1 (Exposure), the attenuated clinical monitoring schedule is a reasonable course of action.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section has been addressed in the prior submission of Lamictal XR for partial seizures (NDA 22115). Dr. Kapcala indicates in his safety review that the clinical pharmacology review of the submission concluded that the evaluation was adequate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The observation interval for lamotrigine has been 15 years since first approval in the US, allowing adequate time for the emergence of post clinical trial adverse events. Therefore no large magnitude unexpected events are anticipated with a long acting form. No additional examination of similar drugs in class is performed to seek insight into the potential for new adverse effects with use of Lamictal XR.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the conduct of the double blind phase of the principal efficacy study LAM30055. There was one death (b) (6) months after withdrawing prematurely from the double blind phase of the study due to hepatocellular cancer. This was in patient 254, a 57 year old male who was reported to have moderate alcoholic cirrhosis and viral cirrhosis 105 days after the start of Lamictal XR. The viral cirrhosis and alcoholic liver disease are clearly not due to Lamictal XR but elevate the risk of hepatocellular carcinoma. This death is confounded by the concomitant liver disease of viral and alcoholic cirrhosis and is very unlikely related to the treatment with Lamictal XR. This death was also reviewed for the submission of NDA 22509.

There were no deaths in the open label continuation of LAM30055. There was one death in the IR monotherapy study, US 30/31, study period April 7, 1994 to August 7, 1996. This occurred in patient 30-1-1039 a 22 year old white male randomized to receive valproic acid pseudoplacebo. After (b) (6) days of treatment with VPA in addition to concomitant phenytoin the patient was found dead and a diagnosis of SUDEP was rendered. This event was reviewed for approval of Lamictal IR for use as monotherapy, NDA 20241

7.3.2 Nonfatal Serious Adverse Events

Table 26 Serious Adverse Events in Lamictal XR studies and Lamictal IR monotherapy studies

Study	SAE %	
LAM30055	250mg = 5% (5)	300mg = 3% (3)
30/31 lamotrigine monotherapy	5% (4) -76 patients randomized to LTG	
All completed monotherapy studies	5.4% (47)	
LAM100034 & LAM100036 pooled	3%	
LEP105972 (planned enrollment n=170)	11.8% (based on planned completed enrollment of 170 patients)	

Principal Efficacy Study – LAM30055

In the double blind phase of Study LAM30055 there were 10 serious adverse events which occurred in 8 subjects. 3 (3%) patients in the 300mg Lamictal XR group and 5 (5%) patients in the Lamictal XR 250mg group reported serious adverse events. Two subjects in each group reported two SAEs. The subject number, brief demographics, study phase at onset, and indication of study drug withdrawn (yes/no) are presented in table 27.

Table 27 Subject Listing of all Serious Adverse Events, LAM30055 DB phase

Subject #:Demographics	Preferred term (Verbatim text)	Study Phase at Onset	Background AED if onset during Conversion	Study Drug With-drawn (Yes/No)	Days on Mono-therapy
Lamictal XR 300mg / day group					
807: 24y/F/White	Brain neoplasm (Brain tumor)	Conversion	Pregabalin	Yes	
522: 14y/M/White	Grand mal convulsion (Acute seizure exacerbation [generalized tonic-clonic]) (b) (6) days after lamotrigine	Monotherapy	---	No	(b) (6) days on mono-therapy)
	Respiratory failure (Ventilator failure) -diastat	Monotherapy	---	No	
62: 25y/M/White	Head injury (Trauma craniocerebral) seizure day (b) (6) with head trauma, still on background AED	Conversion (day (b) (6) up titration of LTG, BKG unchanged)	Valproate	No	
Lamictal XR 250mg/day group					
810: 29y/M/African American	Concussion (Possible concus[s]ion) Seizure while driving with MVA, during monotherapy, day (b) (6)	Monotherapy	---	No	(b) (6) days on mono-therapy)
821: 42y/F/White	Upper GI hemorrhage (Upper GI bleed)	Monotherapy	---	No	
223: 33y/F/Asian	Pyrexia (Fever)	Conversion	Oxcarbazepine	Yes	
	Rash (skin rash)	Conversion	Oxcarbazepine	Yes	
254: 56y/M/Asian	Hepatic neoplasm malignant (Hepatocellular cancer)	Monotherapy		Yes	
255: 52y/M/Asian	Partial seizures with secondary generalization (Partial seizures evolving to secondarily generalized seizures) recurrent seizures at initiation of background AED dose reduction.	Conversion (taper of BKG med, day (b) of 80%)	Oxcarbazepine	No	
	*shaded rows represent seizure related adverse event				

Four of the 8 serious adverse events involved convulsive activity (patients 522, 62, 810, 255). Two occurred during conversion phase (patient 62, 255) and two during monotherapy phase (810, 522). The epileptic events on monotherapy occurred when the patients were on Lamictal XR therapy alone for 31 days (patient 522) and 64 days (patient 810). In two cases the seizure events occurred during the conversion phase. In one case the event occurred during Lamictal XR dose escalation (patient 62) while background AED therapy remained unchanged. In the second case (patient 255) the subject was on the 3rd day of background dose reduction at 80% of original dose. In this second case the reduction of the background AED may be implicated in the seizure event.

There was one SAE of rash, which is in boxed warning in proposed labeling. The remaining three SAEs, brain neoplasm, upper GI bleeding, and hepatic neoplasm (with background viral cirrhosis) were not likely related to study drug treatment.

LAM30055 Open Label Phase

Four subjects (2%) experienced 5 SAEs during the open label continuation phase of Study LAM30055. During this phase all subjects are receiving Lamictal XR 300mg daily.

One patient tripped, fell and suffered a Periorbital hematoma, there was no apparent seizure. A second patient (62) had a seizure during the night and fell (b) (6) days after beginning open label Lamictal XR, the patient suffered closed head injury. A third patient was struck by a motor vehicle when stepping off of a bus. The fourth patient was a baseline failure subsequently enrolled into open label therapy, approximately (b) (6) weeks after beginning Lamictal XR treatment the patient developed status epilepticus and was hospitalized. The patient's baseline AED was Trileptal which had been reduced from 2400mg a day to 600mg a day by the time of the status epilepticus event. This event may have been related to background AED withdrawal.

Reviewer Comment: The percent of SAEs is comparable among the Lamictal XR studies and between the Lamictal XR and Lamictal IR monotherapy studies. The composition of SAEs differs between Study LAM30055 and Study 30/31 (Lamictal IR monotherapy study). In Study LAM30055 there were 4 SAEs due to seizure or seizure related traumatic injury while in Study 30/31 (Lamictal IR monotherapy) there were no SAEs due to seizure. In study LAM30055 two of the seizure related SAEs occurred in conversion phase while two were in monotherapy phase. The event of primary interest is the seizure during monotherapy in the 300mg/day treatment group which raises concern of that 300mg/ day may be an insufficient dose for monotherapy, especially in light of the absence of epilepsy related SAEs in study 30/31. This case was counted as an escape and therefore contributes to the efficacy analysis which mitigates this concern. The remainder of the convulsive events occurred either in the low dose, 250mg/day group, or while the background therapy was maintained.

Of the remaining 4 SAEs no causality can be established for the two cases of neoplasm or the GI bleed. The remaining case of rash is currently an adverse event in labeling.

7.3.3 Dropouts and/or Discontinuations

Table 28 Study Withdrawals in Lamictal XR and Lamictal IR monotherapy studies

Study	Dropout %	
LAM30055	250mg = (11)10%	300mg = (4) 4%
30/31 lamotrigine monotherapy	20%	
All completed monotherapy studies	13.4 %	
LAM100034 & LAM100036 pooled	5%	
LEP105972 (planned enrollment n=170)	13.5% (based on planned completed enrollment of 170 patients)	

The discontinuation rate in study LAM30055 was greater in the 250mg treatment arm, 11 cases (10%) compared to the 300mg / day treatment arm, 4 cases (4%). In the 250mg, lower dose group, breakthrough due to seizure is a concern however only one case was due to a seizure, 7 were due to rash, which is counterintuitive in this lower dose group.

The discontinuation rate is notably lower in study LAM30055 compared to the Lamictal IR monotherapy studies but in the 250mg /day group, the rate is somewhat greater than the Lamictal XR studies in partial (LAM00034) and primary generalized tonic clonic seizures (LAM00036). The 300mg / day group discontinuation rate is comparable to the Lamictal XR studies in partial and primarily generalized seizures, table 29. This comparability mitigates concern of a unique safety signal in the use of Lamictal XR in monotherapy.

Among those who discontinued Lamictal XR in both the 300mg and 250mg / day treatment group, 8 discontinued due to rash and 4 of these patients were on concomitant valproic acid. Two patients discontinued due to neoplasm, one due to Arthralgia, one due to anxiety, one due to dizziness – nausea, one due to simple partial seizures and one due to Hand-foot-and-mouth disease.

Table 29 Listing of TEAEs Leading to Withdrawal for the Principal Efficacy Study – LAM30055

Lamictal XR 300mg / day group (n= 113)					
Subject #	**AGE**	**RACE**	**SEX**	**Preferred Term**	**Serious Y/N**
8	34	White	F	Anxiety	N
318	36	White	M	Joint swelling	N

Lamictal XR 300mg / day group (n= 113)					
Subject #	**AGE**	**RACE**	**SEX**	**Preferred Term**	**Serious Y/N**
				Arthralgia	N
633	45	African American	F	Rash	N
807	24	White	F	Brain neoplasm	Y
Lamictal XR 250mg / day group (n=113)					
9	49	White	M	Dizziness	N
				Nausea	N
16	19	White	F	Rash	N
71	51	White	F	Rash	N
112	24	White	M	Rash	N
153	22	White	F	Rash	N
154	43	White	F	Rash	N
220	36	Asian	F	Rash	N
223	33	Asian	F	Pyrexia	Y
				Rash	Y
254	56	Asian	M	Hepatic neoplasm malignant	Y
301	27	African American	M	Simple partial seizures	N
805	39	White	F	Hand-foot-and-mouth disease	N

Reviewer Comment: The dropout rate for the 300mg / day group is similar to the dropout rate of Lamictal XR studies from the application packages for use of Lamictal XR as adjunctive therapy. The dropout rate for the 250mg / day group is notably higher. The reason for this elevated dropout rate in the low dose group is unclear. Only one case was due to seizure which is the intuitive reason which might be expected to occur in a lower dose group. The most frequent reason for dropout in the 250mg / day group is rash which is less expected in a low dose group. Three of the seven patients who developed rash were on concomitant valproic acid which may explain an increased likelihood of rash in approximately 40% of the patients that developed rash in the 250mg / day group. (b) (4) .

Overall the dropout rate in studies of Lamictal XR is lower than Lamictal IR monotherapy studies.

7.3.4 Significant Adverse Events

Skin Rash

Serious skin rash is the most threatening adverse effect in the use of Lamictal. This risk is well defined and present in a boxed warning. In this section the frequency of rash in

study LAM30055 is compared with the occurrence of rash in study 30/31 and the completed monotherapy studies.

Principal Efficacy Study – LAM30055

In Study LAM30055, rash was reported by 4 (4%) subjects in the 300 mg/day LTG XR group and 12 (11%) subjects in the 250 mg/day LTG XR group. Most TEAEs of rash were judged to be reasonably attributable to study drug in both treatment groups. Additionally, rash led to withdrawal of 1 (<1%) subject in the 300 mg/day LTG XR group and 7 (6%) subjects in the 250 mg/day LTG XR group. During the long term continuation phase of study LAM30055 two subjects reported rash.

Study 30/31

10 (13%) subjects in the Lamictal IR treatment group experienced rash and 6 (7.5%) in the pseudoplacebo (VPA) group. One of the cases in the Lamictal IR group was diagnosed as Stevens-Johnson Syndrome. 8 of the 10 rashes in the Lamictal IR group were considered mild to moderate intensity while 2 sere considered severe. Eight of the rashes in the Lamictal IR group occurred during treatment transition, which is the most likely interval of onset. Six patients in the Lamictal IR group and 1 in the pseudoplacebo (VPA) group discontinued due to the rash. All serious rashes and rash leading to discontinuation in the Lamictal IR group occurred during treatment transition phase of the study.

Completed Monotherapy Studies (Lamictal IR, including study 30/31)

Of the 868 unique subjects exposed to LTG IR in the Completed Monotherapy Studies, 117 (13%) reported an AE classified as “all rash” (rash, pustular rash, macular papular rash, urticaria, Stevens-Johnson Syndrome, and vesicular bullous rash). Most (100/117, 85%) of the rashes were mild to moderate in intensity. Seventeen rashes on LTG IR were considered severe, 8 were SAEs, and 53 lead to discontinuation of LTG IR.

Reviewer Comment: The frequency of rash in study LAM30055 is at a maximum in the 250mg/day group. At this maximum the frequency is less than the frequency in the Lamictal IR monotherapy trials. No SJS or TEN developed in study LAM30055.

SUDEP

There were no deaths in study LAM30055. In the completed IR monotherapy studies there were 7 deaths, 4 were on study medication, 3 were on a comparator AED. Among those on Lamictal IR two were classified as SUDEP. These events both occurred during stable monotherapy dosing for 300 days in one case and 355 days in the second. There was a SUDEP case in the VPA arm of study 30/31 which occurred approximately 1 month after the addition of the VPA pseudoplacebo. This latter case supports the ethical concern of pseudoplacebo which was put forward in the White Paper, see section 2.6

7.3.5 Submission Specific Primary Safety Concerns

none

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Principal Efficacy Study – LAM30055

A total of 53% (59) of patients in the 300mg / day Lamictal XR group and 61% (68) of patients in the 250mg / day group experienced an adverse event. The most common AEs for the LTG XR 300 mg/day group were headache (26%), dizziness (11%), nasopharyngitis (6%), and nausea (5%). The most common AEs for the LTG XR 250 mg/day group were headache (28%), rash (11%), dizziness (9%), nasopharyngitis (6%), insomnia (5%), nausea (5%), and somnolence (5%). The incidence of AEs was similar between the 2 treatment groups with the exception of rash and insomnia which were less common with LTG XR 300 mg/day (4% and 0%, respectively) relative to LTG XR 250 mg/day (11% and 5%, respectively), table 30.

Table 30 Most Common (Reported by At Least 5% of Subjects in Either Treatment Group) Treatment-Emergent Adverse Events (Safety Population: Study lAM30055)

	LTG XR 300 mg/day N=112	**LTG XR 250 mg/day N=111**
Any AE, n (%)1	**59 (53)**	**68 (61)**
Preferred Term, n (%)		
Headache	29 (26)	31 (28)
Dizziness	12 (11)	10 (9)
Rash	4 (4)	12 (11)
Nasopharyngitis	7 (6)	7 (6)
Nausea	6 (5)	6 (5)
Somnolence	5 (4)	6 (5)
Insomnia	0	5 (5)

Adverse Events by Study Phase at Onset

Adverse events overall were more common during the Conversion Phase relative to the monotherapy phase for both the 300mg/day and 250mg / day treatment groups. The preferred terms which were most frequent during the Conversion Phase for both

treatment groups were dizziness, somnolence, rash, and nausea. There was no consistent trend seen in the incidence related to study phase for headache, n nasopharyngitis, or insomnia. The incidence of AEs was consistently lower for the LTG XR 300 mg/day group relative to the 250 mg/day group regardless of study phase at onset.

Study 30/31

A total of 63 subjects (83%) in the LTG group and 69 subjects (86%) in the VPA group (low dose active control- pseudoplacebo) reported AEs.

The five most commonly reported AEs in the Lamictal IR treated group in this study were dizziness (24%), nausea (18%), headache (17%), asthenia (14%), and tremor (11%).

Completed Lamictal IR Monotherapy Studies

A total of 605 (69.7%) subjects on LTG reported AEs some time during the course of treatment. The five most commonly reported AEs were headache (16.7%), asthenia (13.6%), "all rash (13.5%), dizziness (12.7%), and nausea (9.1%).

Reviewer Comment: Study LAM30055 had fewer total adverse events than the immediate release studies, 53% , compared to 83% in study 30/31 and 69.7% in the pooled Lamictal IR monotherapy studies. The profile of adverse events which occurred in at lease 5% of patients was similar. In study LAM30055 headache was the most frequent at 26% compare to 13% in study 30/31 and 17% in all pooled IR monotherapy trials. In Study LAM30055 there was a 6% frequency of Nasopharyngitis in the 300mg/day group whereas this adverse effect did not occur at a rate greater than 5% in either study 30/31 or the pooled IR (immediate release) monotherapy studies. Dizziness and nausea were less frequent in LAM30055 compared to study 30/31 or the pooled IR monotherapy studies.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were not conducted prospectively in Study LAM30055. Because of the extensive database of clinical laboratory data from adjunctive studies with LTG-IR, including the absence of laboratory findings in the previous conversion to monotherapy study with LTG (Study US 30/31), clinical laboratory tests were performed at screening only to confirm eligibility- agreed upon at teleconference with sponsor on July 24, 2009.

7.4.3 Vital Signs

Vital signs and ECG data were not collected prospectively during treatment in Study

LAM30055. Because of the extensive database of vital signs and ECG data from adjunctive studies with LTG-IR, including the absence of safety findings in the previous conversion to monotherapy study with LTG (Study US 30/31), vital signs and ECG were performed at screening only to confirm eligibility- - agreed upon at teleconference with sponsor on July 24, 2009.

7.4.4 Electrocardiograms (ECGs)

ECG not collected prospectively - agreed upon at teleconference with sponsor on July 24, 2009.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies submitted in this application.

7.4.6 Immunogenicity

Lamotrigine is a small molecule however immunogenicity of lamotrigine has manifested in the occurrence of serious rash. This has been well characterized in lamotrigine IR which was approved in 1994. The threat of this immunologic response currently has a boxed warning in labeling. In study LAM30055 the frequency of rash has been less than in Lamictal IR study 30/31 seen to be 11% (11% in 250mg/day group and 4% in 300mg/day group) 13% respectively. In study 30/31 one case developed into Stevens-Johnson syndrome whereas non in study LAM30055 developed Stevens-Johnson syndrome or Toxic Epidermal Necrolysis.

7.5 Other Safety Explorations

This safety dataset for efficacy supplement for Lamictal XR is composed of pivotal clinical trial LAM30055, legacy Lamictal IR monotherapy trials, and ongoing trial (b) (4). All but ongoing study (b) (4) were reviewed in NDA22509 (LAMICTAL® XR™ (lamotrigine) Extended-Release Tablets for Adjunctive Treatment of Primary Generalized Tonic-Clonic Seizures), therefore NDA22509 is referenced for this section.

7.5.1 Dose Dependency for Adverse Events

See section 7.5 opening statement

7.5.2 Time Dependency for Adverse Events

See section 7.5 opening statement

7.5.3 Drug-Demographic Interactions

See section 7.5 opening statement

7.5.4 Drug-Disease Interactions

See section 7.5 opening statement

7.5.5 Drug-Drug Interactions

See section 7.5 opening statement

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Non-clinical studies are not submitted with this application; however the currently approved label for Lamictal XR (section 13.1) cites previously performed carcinogenicity studies. One mouse and two rat studies following oral administration of lamotrigine for up to two years at maximum tolerated doses were performed; no evidence of carcinogenicity was seen.

7.6.2 Human Reproduction and Pregnancy Data

In the LTG XR clinical development program, there were 6 pregnancies that occurred: 4 in Study LAM100036, 1 in Study LAM30055 (normal birth), and 1 in Study LAM10005. One of the pregnancies resulted in a spontaneous abortion, which was considered reasonably attributable to study drug. The outcome for the other pregnancies included 2 healthy normal neonates, 2 elective terminations of pregnancy, and 1 unknown outcome.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were 32 patients in enrolled in the age range 13 to 17 inclusive. Twenty of the pediatric age range subjects experienced 65 adverse events. One pediatric patient suffered an SAE; none were withdrawn from the study. The subject (522), who experienced the SAE, noted in table 23, suffered an exacerbation of seizures and developed respiratory failure, possibly due to a Diastat treatment.

Table 31 Adverse events in the pediatric population of study LAM30055

Perferred term	Frequency	Percent of All AE
Headache	29	44.6
Nasopharyngitis	3	4.6

Nausea	3	4.6
Pharyngitis	3	4.6
Abdominal pain upper	2	3.1
Rash	2	3.1
Rhinitis allergic	2	3.1
Seasonal allergy	2	3.1
Abdominal pain	1	1.5
Alopecia	1	1.5
Amnesia	1	1.5
Bronchitis	1	1.5
Cough	1	1.5
Diarrhoea	1	1.5
Dysmenorrhoea	1	1.5
Epistaxis	1	1.5
Gastrooesophageal reflux disease	1	1.5
Grand mal convulsion	1	1.5
Muscle spasms	1	1.5
Pain in extremity	1	1.5
Pharyngotonsillitis	1	1.5
Respiratory failure	1	1.5
Tachycardia	1	1.5
Tonsillitis	1	1.5
Tremor	1	1.5
Upper limb fracture	1	1.5
Vomiting	1	1.5

Table 32 Adverse events in the pediatric population of study LAM30055 by dose group

	LTG XR 300 mg/day N=112	**LTG XR 250 mg/day N=111**
Any AE, n (%)1	**59 (53)**	**68 (61)**
Preferred Term, n (%)		
Headache	29 (26)	31 (28)
Dizziness	12 (11)	10 (9)
Rash	4 (4)	12 (11)
Nasopharyngitis	7 (6)	7 (6)
Nausea	6 (5)	6 (5)
Somnolence	5 (4)	6 (5)
Insomnia	0	5 (5)

Headache was the most frequent adverse event in the pediatric group, 44.6% followed by Nasopharyngitis 4.6%, Nausea 4.6%, pharyngitis 4.6%, abdominal pain upper 3.1%, rash 3.1%, rhinitis allergic 3.1% and seasonal allergy 3.1%. The remaining adverse events accounted for less than 2% each, of the total. This profile is similar to the profile

of common adverse events in adults for the top 5 preferred terms. There is a difference in positions five and six, somnolence and insomnia respectively, where these terms are not present in the list of pediatric adverse events.

Request for Partial Waiver for Conducting Pediatric Studies

The sponsor requests a partial waiver from conducting a study evaluating conversion to monotherapy with LAMICTAL in pediatric patients with partial seizures age 1 month to 16 years who are receiving therapy with a single antiepileptic drug. The sponsor believes that conducting such a trial would not be feasible for ethical reasons a well as the absence of a suitable comparator group.

The sponsor (GSK) provides history which reveals this is the second iteration of such a request for partial waiver. The first directive to pursue a study of the safety and effectiveness of conversion to monotherapy with Lamictal in pediatric patients age 1 month to 16 years (receiving valproate) for treatment of partial seizures came as a Phase IV commitment, triggered by the approval to lift the restriction for converting adults on valproate to LAMICTAL monotherapy (January 14, 2004). In a subsequent correspondence on April 7, 2005 the sponsor noted the ethical issues relevant to studies such as 30-31 which was the basis for approval of monotherapy in adults. In addition GSK noted possible safety issues surrounding the use of valproate in pediatric patients less than age two. The FDA agreed to a partial waiver in patients 1 month to 2 years but denied a waiver for the age range 2 to 16 years.

The sponsor now presents additional counter argument in this second iteration of request for partial waiver from conducting a study to evaluate conversion to monotherapy with LAMICTAL in pediatric patients with partial seizures age 1 month to 16 years old receiving therapy with a single AED. These counter arguments are twofold, first based on current thinking, a pseudoplacebo type study design such as study 30/31 is no longer considered ethical, second, if a design based on the use of a historic control is utilized, such as in study LAM30055, there is no suitable comparator group. The White Paper historic control is based on data obtained from studies in adults. The sponsor also believes that a monotherapy indication in pediatric patient based on extrapolation from adjunctive efficacy and pharmacokinetic data in adults and pediatric patients and monotherapy efficacy and PK data in adults is also not feasible due to the long interval needed to reach steady state monotherapy LAMICTAL level (14 to 15 weeks in patients needing 10mg/kg/day and 8 weeks in patients taking 5mg/kg/day).

Age band for current labeling

> Lamictal IR is approved for monotherapy to ≥16 years of age, while the proposed label for Lamictal XR is for use in conversion to monotherapy in patients ≥13 years of age. This seems to contradict the sponsor request for pediatric wavier from 1 month to 16 years of age, for how can Lamictal XR be labeled down to age 13 when there is a pediatric waiver to age 16?

Study 30/31, studied to age 13 but only 7 patients 17 and less.

Table 33 Number of Pediatric Participants in LAMICTAL IR monotherapy trial (30/31) and LAMICTAL XR Studies (LAM100034, LAM100036, and LAM30055.

Study 30/31	
AGE	Number subjects
13	1
14	1
15	1
16	2
17	2
Study LAM100036	
AGE	Number subjects
13	1
14	5
15	4
16	3
17	6
Study LAM100034	
AGE	Number Subjects
13	3
14	4
15	3
16	1
17	9
Study LAM30055	
AGE	Number Subjects
13	5
14	9
15	4
16	7
17	7

Table 34 Study LAM30055 Pediatric Exposure to LAMICTAL XR (250mg/300mg)

LAM30055 pediatric exposure 250/300mg				
Subject	Age	Exposure	Dose	Comment
134	13	77 days	250mg	

101	13	85	250	
147	13	112	300	
169	13			max 200mg
170	13	84	250	
141	14	83	250	
148	14	113	300	
166	14	84	250	
177	14	84	250	
179	14	84	300	
522	14	64	300	
722	14	55	300	
862	14	133	250	
140	15	84	300	
144	15	83	300	
145	15	76	300	
167 **Total Exposure**	15	112 1413 total days exposure	300	 630 days at 250mg (7 patients) 783 days at 300mg (9 patients)

Safety of Lamictal XR in monotherapy is supported to age ≥13 based on the currently labeled approval of Lamictal XR "as adjunctive therapy for primary generalized tonic-clinic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age."

Efficacy is not supported for use of Lamictal IR conversion to monotherapy for age <16 in current labeling. Study 30/31 had only 3 patients in this age range.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

In this submission the sponsor provides the following narrative on overdose:

"In Study LAM30055, an overdose of LTG XR was defined as an ingestion of a dose ≥5 times the target daily dose indicated by the protocol. No overdose of LTG XR was reported during the study.

In the LTG XR clinical development program, there was one report of overdose, a summary of which is provided in the initial submission of NDA 22-115. A subject in the LTG-LTG treatment group in the open-label Continuation Phase of Study LAM100034 was taking 200 mg/day LTG XR and had a fatal SAE of "acute poisoning by LTG". The

event was judged by the investigator to have a reasonable possibility of being related to study drug. The investigator indicated that the “acute LTG poisoning” represented a possibly intentional LTG overdose, although there was no circumstantial evidence suggesting an intentional overdose with LTG, and the event did not meet the protocol definition of overdose. Concomitant medications included VPA and clonazepam. No incidences of targeted overdose with LTG XR in the LTG XR clinical development program were reported.

There were no reports of overdose with LTG IR during Study US 30/31 or the individual studies in the Completed Monotherapy Studies grouping (US 30/31, UK 49, UK 74, UK 89, UK 105, UK 106, UK 111, UK 112, UK 115).

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose of LTG IR has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, and coma.”

Drug Abuse

The abuse and dependence potential of Lamictal have not been evaluated in human studies.

Withdrawal and Rebound

The possibility of withdrawal and rebound were not assessed for LTG XR during the Lamictal XR clinical development program.

The current Lamictal XR label indicates in section 5.8, Withdrawal Seizures; “*As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of at least 2 weeks (approximately 50% reduction per week)*

7.7 Additional Submissions / Safety Issues

No additional submissions for review

8 Postmarket Experience

Lamictal XR Distribution data for the interval May 29, 2009 to July 24, 2010 (Annual Report) is provided in table 27. Analysis of the sale and distribution of tablets, not including starter kits and samples, reveal distribution of product sufficient to treat (b) (4) patients with 400mg of Lamictal XR daily, over the report interval of 421 days (1.15 years).

APPEARS THIS WAY ON ORIGINAL

Table 35 Lamictal XR Distribution data for the interval May 29, 2009 to July 24, 2010

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

Lamotrigine, the active pharmaceutical ingredient of Lamictal XR has extensive post marketing exposure since approval in 1994. In the most recent annual report for the period covering July 25, 2009 to July 24, 2010, for Lamictal (immediate release lamotrigine) the distribution data for tablets, not including multi-strength starter kits, indicate a total distribution of (b) (4) ,500mg. This represents adequate product to treat (b) (4) patients for one year with 400mg of Lamictal daily.

8.1 For a post-marketing update to November 11, 2009 the reader is referred to the medical review of NDA22509. The following review will bring the post marketing review of Lamictal IR and Lamictal XR up to date from November 1, 2009.

Lamictal XR

AERS Examination, Generic term lamotrigine

The AERS database is examined for cases by preferred term for the interval from the end of post marketing review for NDA22509 (November 19, 2009) to January 14, 2011. The top ten preferred terms present in AERS reports for all forms of lamotrigine are; rash, convulsion, drug exposure during pregnancy, drug ineffective, pyrexia, dizziness, headache, Stevens-Johnson's Syndrome, Product substitution issue, and drug interaction seen in table 28. A parallel evaluation of the AERS database using Empirica Signal reveals the number of cases identified by Empirica Signal and the associated EB05 score, table 36. The AERS search reveals frequencies which are consistently higher, this is because the Empirica search is for one calendar year, compared to the 14 month interval for the AERS search and the Empirical database is processed to remove duplicate entries.

Table 36 Top Ten Preferred terms (11/19/2009 to 1/14/2011) captured from term "lamotrigine"

Top Ten Preferred terms (11/19/2009 to 1/14/2011) PT	AERS # Cases with PT	Empirica # cases 2010 (database query on 1/14/2011	2010 EB05
Rash - *black box	511	448	8.13
Convulsion - *status epilepticus in warnings & precautions / seizure worsening in patient information	349	276	3.8
Drug Exposure during pregnancy	304	233	2.82
Drug Ineffective	211	201	0.79

Pyrexia - *fever is noted in clinical trials more frequently in treatment than placebo	200	167	2.16
Dizziness	167	143	1.07
Headache	156	122	1.01
Stevens-Johnson Syndrome- *black box	143	126	11.49
Product Substitution issue	130	90	7.20
Drug Interaction	129	99	3.05
* Shaded cells represent EB05 greater than 2.0			

Reviewer Comment: In the table of top ten preferred terms for all forms of lamotrigine there are several with EB05 >2 which are events directly related to the API. These include Rash, Stevens Johnson syndrome, convulsion and pyrexia. All of these events are currently in labeling, the specific labeling entry is provided at the asterisk.

The AERS database is also examined for cases of special interest; serious skin rash, hypersensitivity reactions, blood dyscrasias, liver dysfunction, and suicide events for the interval from the end of post marketing review for NDA22509 (November 19, 2009) to January 14, 2011. The number of cases for each of the preferred terms in the category of special interest found in the AERS database, by an Empirica signal search and the associated EB05 are seen in table 37. The EB05 values are notably elevated only for serious skin rashes, toxic epidermal necrolysis and erythema multiforme in the table below and Stevens-Johnsons Syndrome in the table of top ten preferred terms above. There is a modest EB05 elevation of 2.14 noted for “hepatic enzyme increased”.

Table 37 Preferred terms for Events of special interest (11/19/2009 to 1/14/2011), captured from term “lamotrigine”

Preferred terms for Events of special interest (11/19/2009 to 1/14/2011)	AERS # Cases with PT	Empirica # cases 2010 (query on 1/14/2011	2010 EB05
Toxic epidermal necrolysis- black box	37	35	7.62
Erythema multiforme –rare erythema multiforme in clinical trials	13	12	3.27
Completed Suicide	86	69	1.45
Suicide attempt	44	31	1.07
Suicidal ideation	62	47	0.99
Hepatic Enzyme abnormal	2	2	0.68
Hepatic enzyme increased-liver function tests abnormal (adverse events in all clinical trials)	22	21	2.14
Hepatic failure	7	7	1.31

Hepatic function abnormal	24	21	1.69
Neutropenia	14	10	0.66
Leukopenia	15		1.59
Thrombocytopenia	22		1.29
Agranulocytosis	2	2	0.97
Anaemia	12	10	0.62
Aplastic anaemia	3		2.15
aplasia pure red cell	1	1	0.64
Granulocytopenia	2	1	0.08
Pancytopenia	15	10	0.97
Drug hypersensitivity	33	24	1.5
Hypersensitivity	49	39	1.16
Multi-organ failure	12	8	1.05
* Shaded cells represent EB05 greater than 2.0			

Reviewer Comment: Those adverse events of special interest for lamotrigine with an EB05 >2 are present in labeling. The location in labeling is noted.

Disproportionality Evaluation (MGPS) 2009 compared to 2010 for lamotrigine

In this section a disproportionality evaluation is performed for topics of special interest to determine if there has been an increase in signal for these topics with progression from year 2009 to 2010. The search terms for each topic of special interest is presented below.

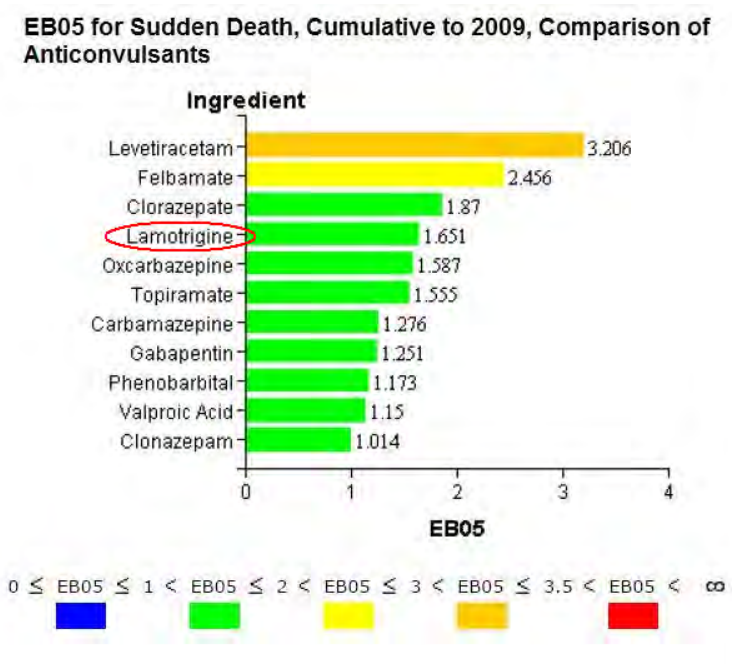
Table 38 lamotrigine safety topics of special interest

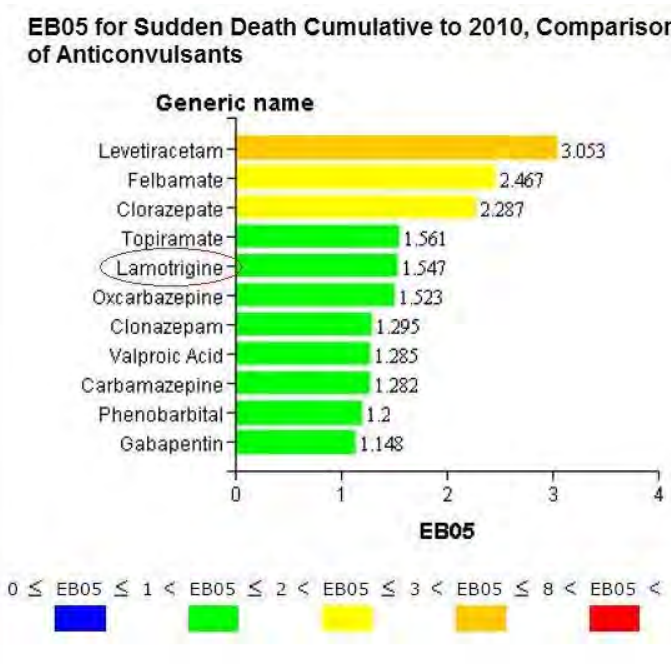
Topic of interest	Search Terms (PTs)
Suicide	Completed suicide, Depression suicidal, Suicidal behaviour, Suicidal ideation, Suicide attempt, intention overdose
Serious Rash	Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
All Rash	Rash
hypersensitivity	hypersensitivity, drug hypersensitivity, DIC, and multi-organ failure
Blood dyscrasia	agranulocytosis, anaemia, aplastic anaemia, aplasia pure red cell, granulocytopenia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia
Hepatic dysfunction	Acute hepatic failure, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Biopsy liver abnormal, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Chronic hepatic failure, Hepatic enzyme increased, Hepatic function

Topic of interest	Search Terms (PTs)
	abnormal, Hyperbilirubinaemia, Liver function test abnormal

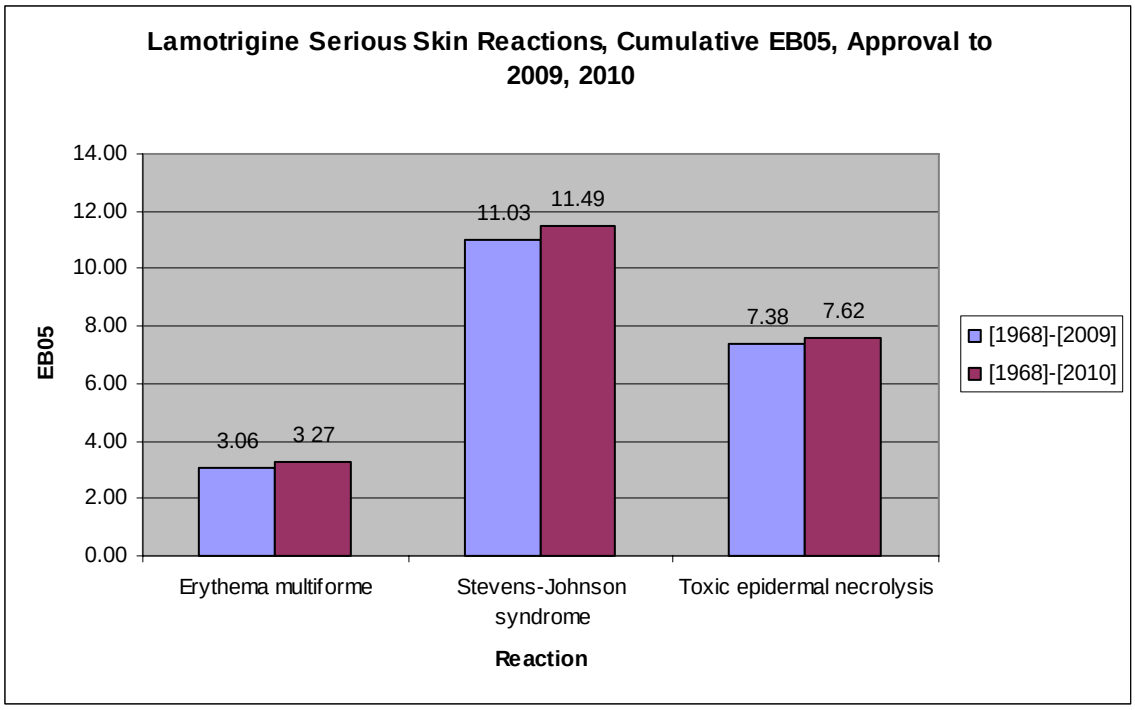
In the graphic below a disproportionality evaluation is performed using the preferred term sudden death for lamotrigine and a panel of commonly prescribed anticonvulsant drugs for the years 2009 and 2010 to assess for any progressive increase in signal with the progression of time. In this analysis the EB05 for lamotrigine remains stable and has a shift in position from 4th to 5th in EB05 value, in addition the EB05 remains below 2.0. This analysis does not indicate a change in the safety signal for sudden death.

Sudden Death

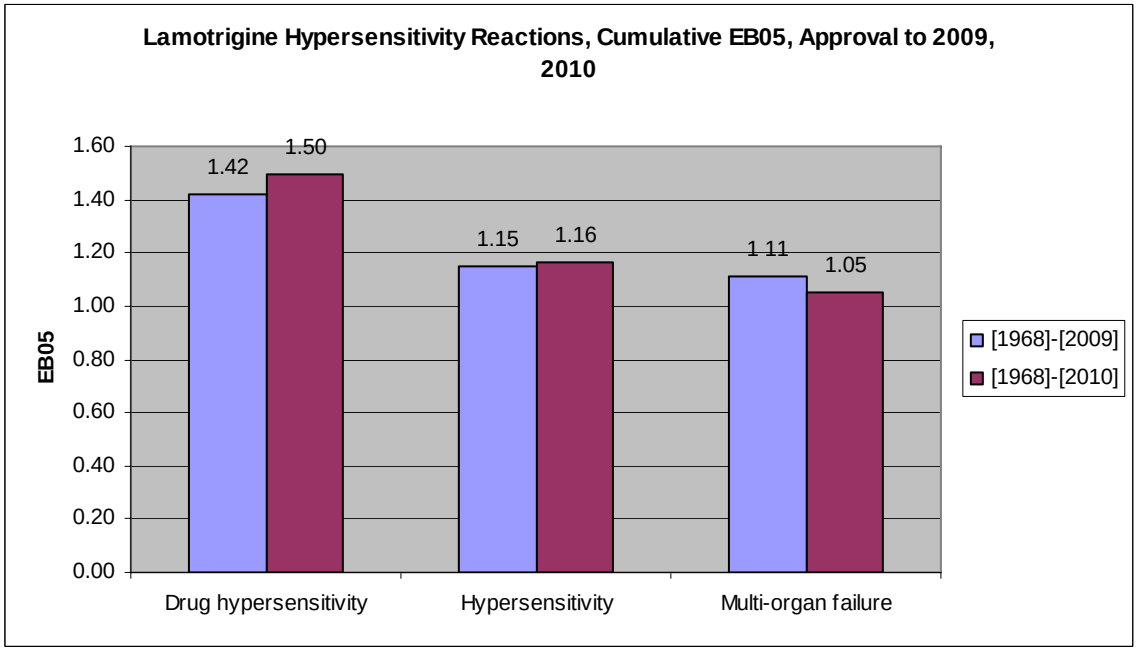




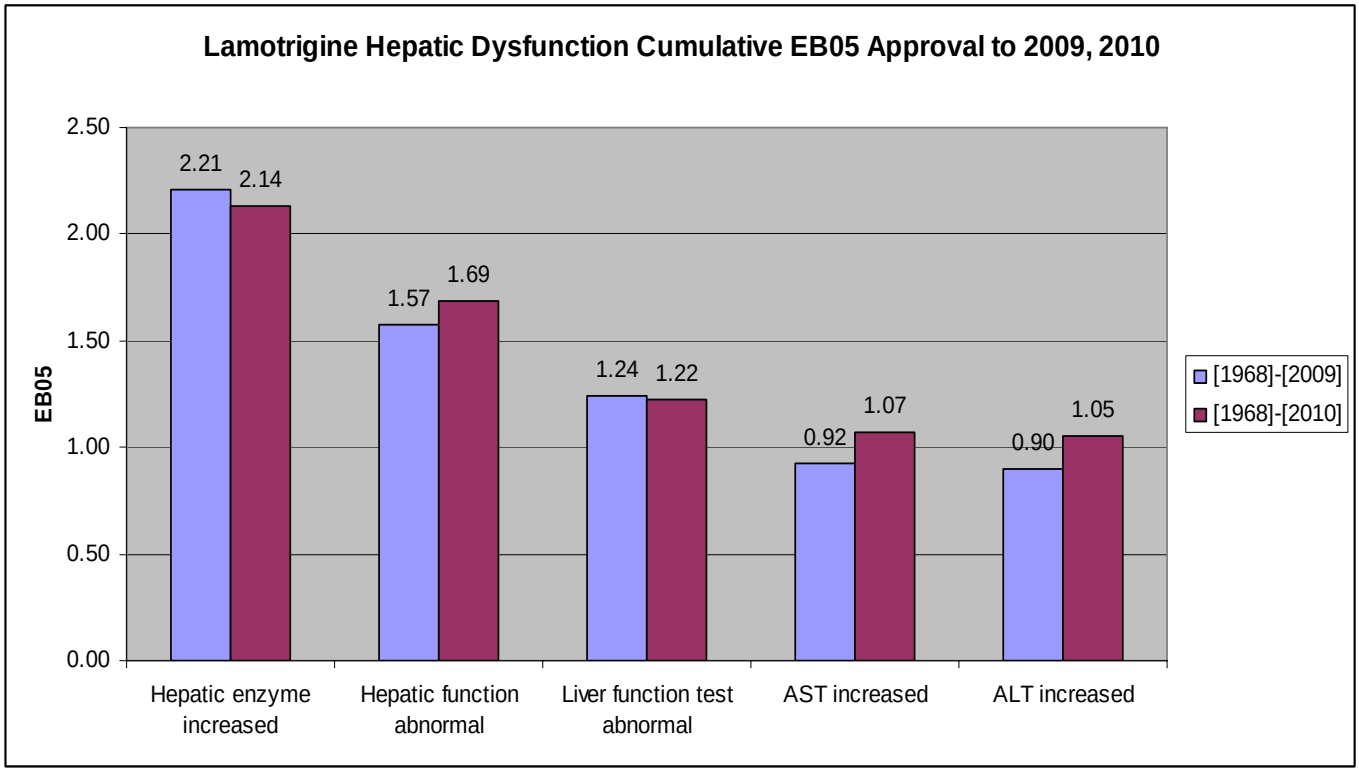
Serious Skin Reaction



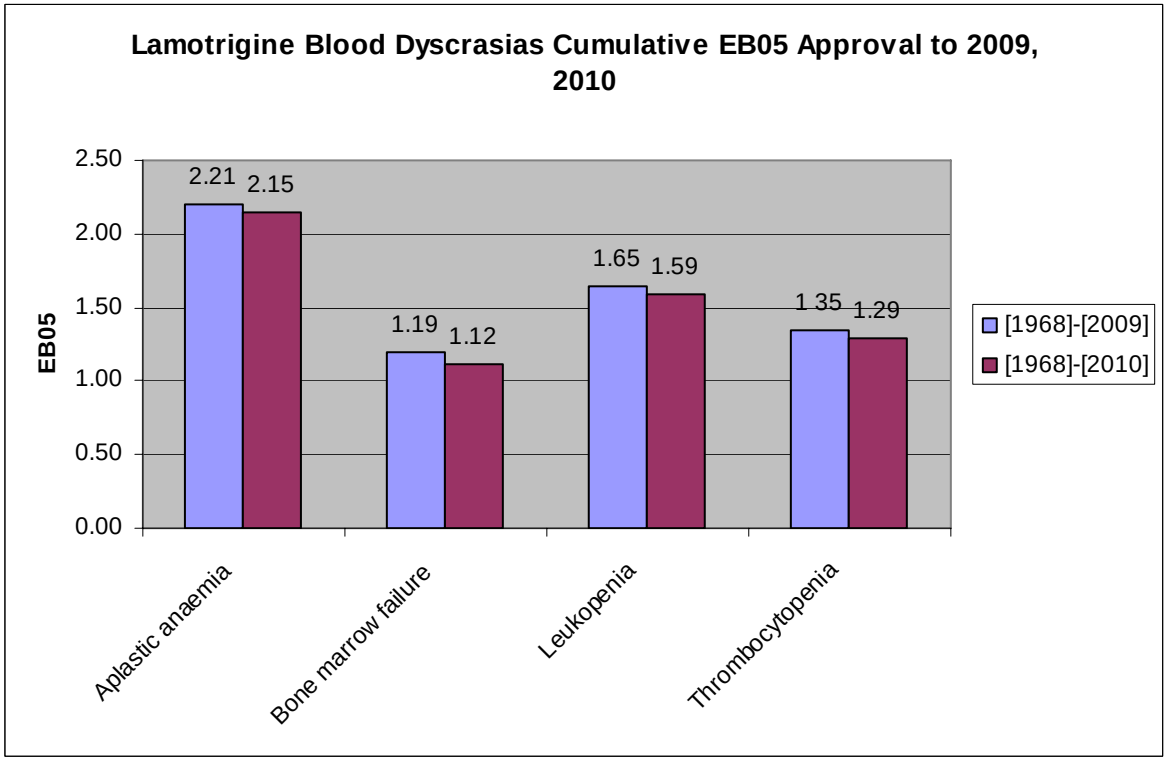
Hypersensitivity Reactions



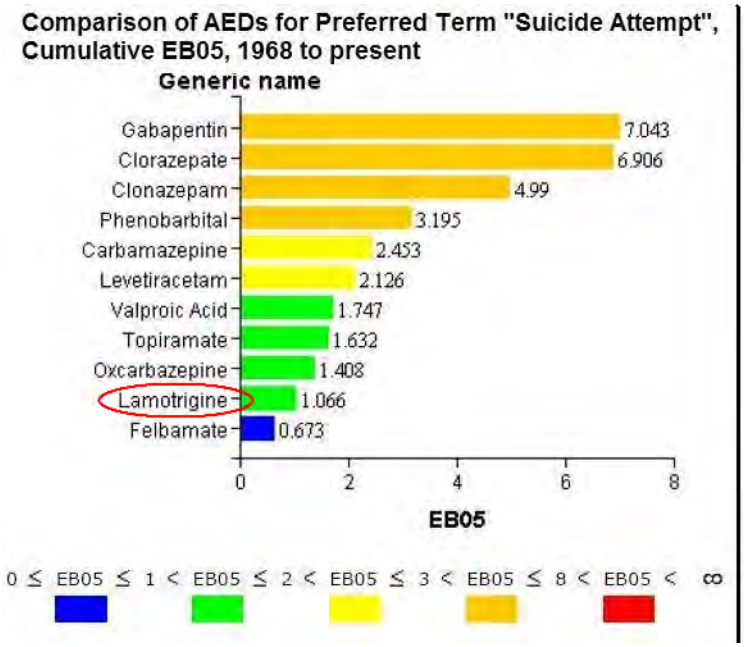
Hepatic Dysfunction

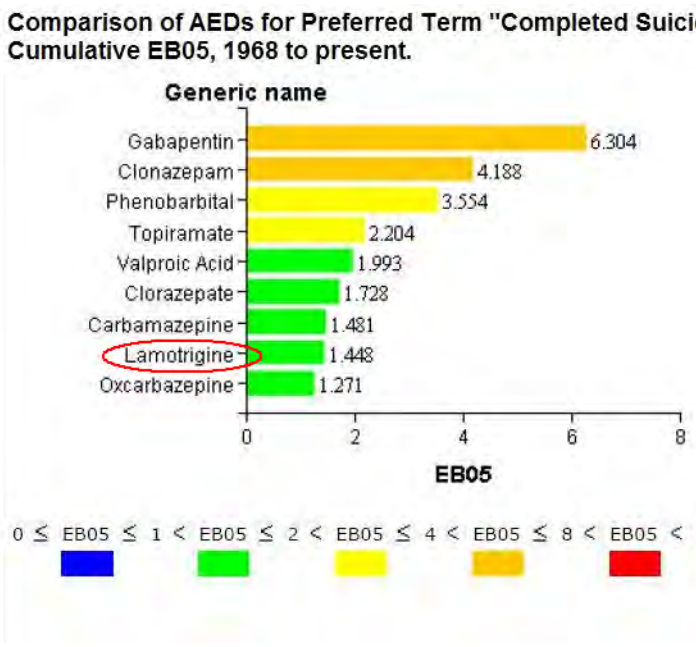


Blood Dyscrasias



Suicide





Reviewer Comment: The EB05 values for topics of special interest are examined for change in the year 2009 to year 2010 interval. There are no notable increases identified. The EB05 for lamotrigine, preferred term sudden death is examined relative to a panel of anticonvulsant drugs frequently used in practice for the years 2009 and 2010. The EB05 does not exceed 2.0 and there is no notable difference between 2009 and 2010. The EB05 for lamotrigine, preferred terms “suicide attempt” and “completed suicide” is examined relative to a panel of frequently used anticonvulsant drugs. The EB05 for “suicide attempt” is close to unity (no difference from background) and the EB05 for completed suicide is well below 2.0. In the cases of both “suicide attempt” and “completed suicide” lamotrigine falls in second from last position of all anticonvulsants in the panel in the magnitude of EB05 signal strength. These post marketing analyses do not indicate a signal for an increase in “suicide attempt”, “completed suicide”, or “sudden death” in the recent marketing interval. Analyses of the topics of special interest for lamotrigine also do not show an increase signal for increase frequency in the recent marketing interval.

9 Appendices

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

The sponsor has grouped “headache and migraine” as the most common adverse event in study LAM30055. Exploration of the preferred terms headache and migraine in the adverse event dataset reveal that there were a total of 61 patient who suffered heachace but only 2 of these were migraine. The reviewer concludes that the grouping of “headache and migraine” in the label give the impression that LAMICTAL XR may frequently cause migraine. However migraine is a distinct phenomenon from headache and should be grouped separately.

The adverse event section of the label should be edited to reflect headache (alone) is the most common adverse effect (26%).

9.3 Advisory Committee Meeting

A. Advisory Committee Meeting Held and date

An Advisory Committee was convened Because of the novel methodology of the Historic Control study design the Peripheral and Central Nervous System advisory committee meeting was convened on March 10, to address relevant issues.

Questions to the Advisory Committee

1. Does the Committee believe that placebo-controlled monotherapy studies in patients with partial seizures are ethically acceptable? (YES/NO/ABSTAIN)

Committee Discussion*: As the discussion evolved it was agreed that the question could be better served by informative exploration of the topic and no vote was taken at the conclusion. The committee first requested a clarification of this question, asking if “pseudo-placebo” was included in the question. This question generated discussion on trial designs beyond those of the eight trials White Paper trials. One such design is in epilepsy patients who have been withdrawn from their anticonvulsant treatment during pre-surgical evaluation, another in the situation of a degenerative process where no alternative treatment is available. At the conclusion of discussion the committee agreed that long-term outpatient placebo-controlled or pseudo placebo-controlled trials of the sort demonstrated by the historical control studies presented by French et al. would be ethically problematic in general but may be appropriate in a subset of specific patient subsets or in the short-term inpatient setting when there is already demonstrated efficacy as adjunctive therapy.*

2. If the answer to Question 1 is No, does the Committee believe that under the specific circumstances, in which a drug is known to be effective as adjunctive treatment, an historical control approach of the sort proposed by French et al., can be acceptable. YES/NO/ABSTAIN

YES: 14 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee unanimously agreed that a historical control approach, of the sort proposed by French et al., can be acceptable under the specific circumstances in which a drug is known to be effective as adjunctive treatment.*

3. If the answer to Question 2 is Yes, the Committee should discuss the specific methodology performed by French et al. (e.g. the propriety of combining the eight control groups into a single historical control, the specific statistical approach used to combine the groups, the appropriateness of using a prediction interval and the specific prediction interval used to establish effectiveness) and whether it is acceptable.

Committee Discussion: *The committee voiced concerns regarding the heterogeneity of the methodology utilized by French et al., but concurred that it is acceptable as long as the inherent irregularities are addressed. One committed member felt the 8 studies were not adequately similar and the KM curves were also not close. However; the prediction interval was concluded to be overall adequately conservative. Additionally, some of the committee members felt that it may have been problematic for the escape rates to be pooled into one aggregate rate.*

4. If the methodology is considered acceptable, what elements of a study using this approach are critical to consider, for example:

a. Matching demographics (age, race, duration/severity of epilepsy, nationality, etc.)
b. Initial concomitant AED's
c. Differences in conversion methods
d. Temporal trends in response
e. Dropouts
f. Any other elements

Committee Discussion: *The committee agreed that all of the following elements are important: matching demographics, initial concomitant antiepileptic drugs, differences in conversion methods, temporal trends in response, and dropouts. The greatest concern was demographics, two committee members had international clinical experience and their observations lead to a conclusion that diagnosis and medical practice may not be fully parallel to US medical standards. Background AEDs were also a prominent concern as a source of difference between the historic control and current study populations. One committee member had concern abut the temporal difference between the historic control studies and the more recent current study. It was advised that historical control methodology is not a new field. Criteria were set forth by Pocock SJ[11] and a committee statistician stated that all of these criteria were violated.*

11 Pocock SJ. The combination of Randomized and Historical Controls in Clinical Trials. J Chron Dis.

5. Does the study under consideration fulfill the necessary criteria to allow for a determination of effectiveness? Specifically, we would like the Committee to discuss:

a. Potential for bias due to the fact that all patients are receiving active treatment.
b. Potential bias due to under-reporting of study endpoints.
c. Number of background AED's
d. The comparability of exit criteria in this study and in the historical control
e. U.S. vs. Foreign data

Committee Discussion*: The potential for bias due to the patient and investigator knowledge that all patients are receiving active treatment was a significant concern to the committee. Some members suggested that an additional arm using an active comparator may reduce this bias. The committee speculated that the low initial escape rate may be due to this bias. Underreporting of study endpoints was corrected by calculated escapes based on seizure diary data. Although post hoc, the retrospective analysis of data should be correct. The difference in background AEDs violates the first Pocock criteria. The difference in country of origin of LAM30055 compared to the historic control was a major concern, two committee members reported discernable differences in diagnostic acumen in their personal interactions with some foreign neurologists. The sponsor commented that the primary investigators were selected because they were at the top of their field.*

In conclusion the committee noted that a drug effect was evident despite the uncertainties that were inherent about the open label bias and heterogeneity in the controls because statistical adjustments were made (prediction interval and lower limit 95% confidence interval). However, it was also noted that it is questionable if there is a drug effect if there is a need for preservation of effect.

6. Has the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures? YES/ NO/ ABSTAIN

YES: 10 NO 2 ABSTAIN; 1

a. If "YES", please discuss whether or not the fact that Lamictal IR is approved for monotherapy was critical to the decision.

Committee Discussion*: Note: one committee member was not present for the vote. The majority of the committee agreed that the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures. All of the committee members who voted "YES" stated that the fact that Lamictal IR is approved for monotherapy was critical to their vote. Please see the transcript for details of the Committee discussion.*

1976;29:175-188.

7. Based on the discussions that transpired, the following question was added during the meeting: Assuming there is a very good match between the active treatment group and the historical controls could you consider approval for a monotherapy indication for a drug that had adjunctive efficacy demonstrated but had not been examined in monotherapy using a different formulation/

Committee Discussion: *The committee agreed that they would recommend approval of a drug that had efficacy demonstrated for adjunctive therapy but had not been evaluated for monotherapy (using a different formulation) if there was a good match between the active treatment group and the historical controls. Please see the transcript for details of the Committee discussion.*

9.4 Study Methodology

9.4.1 Inclusion Criteria- acceptable form of birth control:

a. Complete abstinence from intercourse for 2 weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (a minimum of 2 weeks).
b. Consistent and correct use of one of the following methods of birth control:
• Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female subject.
• Any intrauterine device with a documented failure rate of less than 1% per year.
• Double barrier method consisting of spermicide plus a mechanical barrier (e.g., spermicide plus a male condom or a female diaphragm).

NOTE: Women who had had a hysterectomy, tubal ligation, or were post-menopausal were considered to be of non-childbearing potential.

NOTE: A PK interaction has been observed between lamotrigine and estrogen-based oral contraceptives. Therefore, the use of hormonal therapy (e.g., for contraception or hormone replacement therapy) was not allowed.

9.5 Criteria Comparator

Study/ Pub date	Escape Criteria by Study	Matching Properties
1 (1992)	(1) **(3)**an episode of status epilepticus; (2) **(4)**a secondarily generalized tonic-clonic seizure if none had been experienced within 2 years of study entry; (3) (**1**) a 28-day study seizure rate greater than two times the maximum 28-day study seizure rate during baseline (a 28-day period is defined as any four consecutive study weeks);	Does not have # 4 equivalent, removal of 4 leaves Parity **Inherent non-parity before removal of 4**

	(4) **(2)**a 2-day study seizure rate greater than two times the maximum 2-day study seizure rate during baseline; or *(5)* **(3)** an unacceptable increase in the frequency or intensity of seizure activity that did not meet any of the exit criteria but that was, in the opinion of the treating physician, clinically significant	
2 (1998)	1) doubling of average monthly seizure rate; 2) doubling of the highest consecutive 2-day seizure rate; 3) emergence of a new, more severe seizure type; or 4) clinically significant prolongation of generalized tonic-clonic seizures	Parity
3 (1997)	1. a doubling of the average monthly (28-day) baseline seizure frequency, 2. a doubling of the highest 2-day baseline seizure frequency, 3. a single GTCS if none occurred during baseline, 4. Prolongation of generalized seizure duration that was considered serious by the investigator, or serial seizures or status epilepticus of any seizure subtypes.	Criteria #3 could be placed in Criteria 4 in LAM30055 Criteria 4 = criteria 4 in LAM30055 but serial seizures or status epilepticus match "emergence of a new more severe seizure type" – criteria 3 No representation of criteria # 3, emergence of a new more severe seizure type (except for special case of " a single GTCS" The absence of clear 3 would leave contribution from 3 that is not matched here Non-parity with or without criteria 4- **Inherent Non-Parity**
4		
5 (2001)	1) a twofold increase in monthly seizure frequency in any 28-day period relative to the open-label baseline phase; 2) a twofold increase in the highest consecutive 2-day seizure frequency relative to the open-label baseline phase; 3) occurrence of a generalized seizure if none occurred during the open-label baseline phase; or 4) prolongation of generalized seizure duration that, in the opinion of the investigator, required intervention.	Criteria 3 in this study could represent a special case of criteria 3 in LAM30055. "emergence of a new more severe seizure type" is broader and should capture "occurrence of a generalized seizure if none occurred during open label or baseline". This could also satisfy LAM30055 category 4. It could be anticipated that criteria #3 of LAM30055 should capture more than this criteria 3
6 (2000)	1) a twofold increase in partial seizure frequency in any 28-day period compared to baseline; 2) a twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase (patients with a single seizure as the highest 2-day baseline phase seizure frequency exited the trial if three or more seizures occurred during any 2-day period in the double-blind treatment phase); 3) occurrence of a single generalized seizure if none had occurred in the 6 months prior to randomization; or 4) a prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention.	Criteria 4 in this study is roughly equivalent to criteria 3 of LAM30055. Criteria 3 of this study could be captured by criteria 4 of LAM30055 Effect if criteria 4 is censored could be to remove balance to events which would asymmetrically remain in LAM30055 as criteria 3. N**on-parity before and after #4 modification**
7 (1992)	(1) a two-fold increase in average monthly seizure frequency, (2) a two-fold increase in the highest 2-day seizure frequency, (3) a single generalized seizure if none occurred during the baseline period, and (4) a prolongation of generalized seizure duration (serial seizures or status epilepticus) deemed by the investigator to require intervention.	This study criteria #3 could represent a special case of LAM30055 criteria # 3 This criteria # 4 could capture LAM30055 criteria #3 if serial seizures or status epilepticus is considered emergence of new more severe seizure type **Inherent Non parity**

8 (1993)	(1) a doubling in monthly seizure number compared with the average monthly seizure number during the baseline period; (2) a doubling of 2-day seizure number over the worst 2-day period during the baseline (this frequency criterion applied only when two or more seizures had occurred during some 2- day period of the baseline); (3) **(4)** a single generalized tonic clonic tonic clonic seizure, if none had occurred during the baseline; and a significant prolongation of a generalized tonic clonic seizure considered serious by the investigator, **(3)** or serial seizures or status epilepticus of seizure types other than generalized tonic-clonic seizures.	**Parity**
LAM30055	1. Doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. 2. doubling of the highest consecutive 2-day seizure frequency. 3. emergence of a new, more severe seizure type. 4. clinically-significant prolongation of generalized tonic-clonic seizures.	

9.6 Comparison of White Paper Active and Pseudoplacebo Study Escapes

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

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
1	Gabapentin	Gabapentin	70/93 (75)	66/91 (73)	No, dropouts	Primary efficacy

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
	600mg	2400mg			included NS	= time to exit, secondary = completion rate
2	Valproic Acid 1000mg	Lamictal 500mg	51/64 (80)	22/50 (44)	P<.001, dropouts excluded	Primary efficacy = Per protocol % escape
3	Topamax 100mg	Topamax 1000mg			Not calculated for % escape Time to exit, p = 0.002	Primary efficacy= time to exit
4	Not published					
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/40 (100)	30/46 (65)	P=0.0001, dropouts removed	1^0 efficacy = time to exit.
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/45 (93)	14/34 (41)	P<0.0001 Dropouts excluded	1^0 efficacy = % meeting exit
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	P< 0.0001 Dropouts included	1^0 efficacy = % meeting exit
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/50 (78)	18/45 (40)	P<0.001 Dropouts excluded	1^0 efficacy = % meeting exit

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/s/

STEVEN T DINSMORE
04/25/2011

NORMAN HERSHKOWITZ
04/25/2011