CLINICAL REVIEW of NDA

Application Type	NDA [redacted] (Pediatric Written Request) Supplement
Submission Number	20241 (S032), 20764 (S025)
Submission Code	[redacted] 5
Letter Date	11/29/06
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Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	5/29/07
Established Name	lamotrigine
[redacted] Trade Name	Lamictal
Therapeutic Class	Anticonvulsant
Applicant	Glaxo Smith Kline (GSK)
Priority Designation	P
Formulation	Tablets and chewable, dispersible tablets

[redacted]

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- Not applicable [redacted] (b) (4)

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- Not applicable [redacted] (b) (4)

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- Not applicable [redacted] (b) (4)

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

The submission included one controlled, efficacy study (LAM20006 or 20006). The primary objective of this study was to compare the efficacy of lamotrigine as add-on therapy versus placebo in subjects 1 to 24 months of age with partial seizures in a **randomized, withdrawal study design**.

The study (20006) was an international, multi-center study consisting of an open-label period (up to 26 weeks) followed by a parallel, randomized, withdrawal, double-blind, placebo-controlled, phase. Pediatric subjects (1-24 months of age) diagnosed with epilepsy whose partial seizures were uncontrolled by one or more marketed AEDs were eligible for entry into the open-label, uncontrolled phase of the study. lamotrigine was started as an add-on therapy in the Open-Label Phase (OLP) during which lamotrigine dose was titrated to achieve optimal clinical benefit.

Subjects achieving a ≥ 40% reduction from baseline in partial seizure frequency during the last 28 days of the optimization period were randomized (1:1) to either continued lamotrigine treatment or a gradual, blinded withdrawal (25 % total daily dose reduction weekly) of lamotrigine to placebo. Subjects remained in the Double-Blind Phase (DBP) of the study for 8 weeks or until one of the pre-specified escape criteria was met.

A total of 177 subjects were enrolled in the open label phase of the study and 38 subjects were randomized to the double-blind phase of the study.

LAM20007 (i.e. 20007) was an open-label, uncontrolled study (total N = 204 enrolled patients) conducted to provide long-term add-on treatment and to collect long-term safety data in subjects (N = 125) who had previously participated in LAM20006 as well as in pediatric subjects 1-24 months of age who had not received previous treatment with lamotrigine (i.e., lamotrigine-naïve subjects; N = 79). The primary objective of 20007 was to assess the safety and tolerability of LAMICTAL in pediatric subjects with epilepsy. Secondary objectives were to assess the effect of 48 weeks administration of lamotrigine on seizure frequency, determine the pharmacokinetics of lamotrigine in lamotrigine-naïve pediatric subjects (age 1-24 months) with partial seizures, and to provide 48 weeks of additional treatment for subjects who participated in 20006.

A total of 256 patients enrolled in both studies.

1.3.2 Efficacy

Efficacy findings/results are summarized only for study 20006.

Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint of the study was the proportion of subjects meeting any of the escape criteria during the DBP of the study.

Individual efficacy escape criteria were defined as follows:

- 50% or greater increase in monthly partial seizure frequency compared to the frequency of seizures during the Optimization Period. Monthly seizure frequency was computed using the last 4 weeks of the optimization period and the most recent 4 weeks of the DBP. If a subject had not reached 4 weeks in the DBP but had already experienced a total number of seizures =150% of the seizures of the Optimization Period, the subject was considered to have met the escape criterion;
- Doubling of the highest consecutive 2-day partial seizure count observed during the Optimization Period;
- Onset of a new and more severe seizure type;
- Clinically significant worsening of non-partial seizures observed during the Historical Baseline Phase or the Optimization Period;
- The need to use any therapeutic intervention to control seizures; or

- Status epilepticus.

Comparisons between treatment groups with respect to the proportion of subjects who met the escape criteria were performed using a two-tailed chi-square test.

Secondary Efficacy Endpoints

Secondary efficacy endpoints included the following:

- The difference in the time to escape patterns between subjects receiving Lamotrigine and placebo;
- The proportion of subjects achieving a reduction in monthly partial seizure frequency from baseline of =40% at the end of the OLP;
- Percent change from baseline in seizure frequency at the end of the OLP by seizure type;
- The investigators' global evaluation of the subjects' status at the end of the OLP and DBP;
- An "ITT Double-Blind Phase (DBP)" efficacy population defined as all randomized subjects (with subjects allocated to treatment group according to the treatment actually received) who took at least one dose of study medication during the DBP.

Handling of Premature Discontinuation

Subjects who met escape criteria were classified as "treatment failures." Early dropouts (i.e. premature study discontinuations) were analyzed in two ways:

1. In the first Intent-To-Treat (ITT) analysis, both lamotrigine and placebo subjects who prematurely discontinued from the study and who did not meet escape criteria were classified as "treatment failures" in addition to subjects who met escape criteria. This analysis was labeled the "ITT DBP" analysis in all summary tables.

2. In the second ITT analysis, only the lamotrigine subjects who prematurely discontinued from the study for non-AE reasons were classified as "treatment failures" in addition to subjects who met escape criteria. This analysis was labeled the "ITT DBP/Worst Case" analysis in all summary tables.

Disposition of Subjects

A total of 177 subjects from 14 countries were enrolled in the OLP. One hundred thirty-nine (139) subjects prematurely discontinued the OLP phase. The majority of those subjects (80/139) failed to meet the criteria for randomization to double-blind treatment. Some of these patients failed to meet the randomization because the initial randomization criterion was a "response" (i.e. % seizure reduction rate) $\geq$ 40 % - 80 % relative to the historical, "baseline." Subsequently, the randomization criterion was amended (because many patients had "responses" > 80 %) to permit randomization of patients with a "response" that was $\geq$ 40 %.

Thirty eight (38) subjects were randomized to the DBP of the study (19 in each treatment group). Two subjects in the lamotrigine group were prematurely discontinued from the DBP without meeting escape criteria due to protocol violations. Seventeen subjects in the lamotrigine group and 19 subjects in the placebo group completed the DBP of the study. Two additional subjects were excluded from the ITT patient population due to protocol violation, resulting 17 subjects in each treatment groups in the per-protocol patient population.

Demographic Characteristics

Key demographic characteristics for the OLP Population and by treatment randomization for the ITT – DBP Population are summarized below in Table 1. Note that only one subject was in the < 6 months age group and who was randomized to placebo group.

Table 1 Summary of Key Baseline Characteristics

Demographic Characteristic	OLP LAMICTAL (N=177)	ITT – DBP (N=38)	
		Placebo (N=19)	LAMICTAL (N=19)
Gender - n (%)			
Male	92 (52%)	9 (47%)	12 (63%)
Female	85 (48%)	10 (53%)	7 (37%)
Age (months)			
Median	13.17	14.16	13.54
Range	1.0 – 24.0	2.0 - 23.3	6.6 – 23.9
Age group (months)			
<6	28 (16%)	1 (5%)	0
≥6 - ≤12	56 (32%)	6 (32%)	8 (42%)
>12	93 (53%)	12 (63%)	11 (58%)
Race - n (%)			
White	149 (84%)	17 (89%)	17 (89%)
Black	13 (7%)	0	0
American Hispanic	9 (5%)	2 (11%)	1 (5%)
Asian	2 (1%)	0	0
Other	4 (2%)	0	1 (5%)
Weight (kg)			
Median	9.60	10.10	10.00
Range	2.9 – 17.3	4.5 - 13.2	7.1 – 17.3

Source Data: Table 12.4

Baseline Characteristic	OLP LAMICTAL (N=177)	ITT – DBP (N=38)	
		Placebo (N=19)	LAMICTAL (N=19)
Age at First Seizure (Months)			
Median	3.0	3.0	3.0
Range	0 – 20	0 - 12	0 – 15
Duration of Epilepsy (Months)			
Median	7.36	8.53	9.14
Range	0.4 – 23.5	1.0 – 22.7	3.4 – 21.8
Presenting Seizure Types			
Simple Partial Seizures	42 (24%)	4 (21%)	8 (42%)
Complex Partial Seizures	118 (67%)	16 (84%)	10 (53%)
Sec. Generalized Seizures	77 (44%)	6 (32%)	7 (37%)
Generalized Seizures	46 (26%)	6 (32%)	5 (26%)
Seizure Etiology			
Idiopathic	70 (40%)	8 (42%)	3 (16%)
Symptomatic	105 (59%)	11 (58%)	16 (84%)
Missing	2 (1%)	0	0
Concomitant AED Group			
Induced	126 (71%)	14 (74%)	13 (68%)
Non-induced	51 (29%)	5 (26%)	6 (32%)

Source Data: Table 12.5

1. Induced = Enzyme inducing AEDs (EIAED), Non-induced = Non-enzyme inducing AEDs (including VPA alone).

Primary Efficacy Results

The primary efficacy endpoint was the proportion of lamotrigine versus placebo subjects meeting the escape criteria during the DBP of the study. The proportion of subjects who escaped (i.e., treatment failures) during the double blind phase of the study is shown below in Table 2.

Table 2 **Proportion of Subjects Who Met Escape Criteria during the DBP**

	Placebo		LAMICTAL		
Analysis Population	N	Treatment Failures	N	Treatment Failures	p-value[1]
ITT DBP[2]	19	16 (84%)	19	11 (58%)	0.074; 0.151
PP DBP	17	14 (82%)	17	9 (53%)	0.067; 0.141

Source data: Table 13.1

1. p-values: two tailed chi-square test and Fisher's exact test, respectively
2. Two LAMICTAL subjects who did not meet escape criteria but discontinued prematurely were counted as treatment failures in the ITT DBP analysis.

The proportion of treatment failures was greater among subjects receiving placebo compared with those receiving Lamotrigine. The difference between treatment groups did not achieve statistical significance.

Of the pre-defined escape criterion, a "≥ 50% increase in monthly partial seizure frequency"' was most frequently met either alone or with other criteria and accounted for 81% (13/16) of escapes in the placebo group and 67% (6/9) of escapes in the lamotrigine group in the ITT DBP population.

Only the primary efficacy results are described and summarized here (see section 6.1.4 Efficacy Findings for secondary efficacy endpoint results).

Reviewer Efficacy Conclusions

- [redacted] (b) (4)

- Based upon the primary efficacy analysis of the ITT population (confirm by our Statistical Review by Dr. Sharon Yan, ostensibly, this is a failed study which is not statistically significant (p = 0.0737 for chi-square statistic which may not be appropriate because of small sample size; p = 0.151 for Fisher's exact test which may be more appropriate). In agreement with this view, the sponsor acknowledges that the difference in treatment failures for the ITT analysis of the randomized phase did not achieve statistical significance (p = 0.07).

- Overall, my numerous concerns outlined in my Reviewer Comments about the study design, conduct, and analysis of the controlled trial phase of study 20006 do not allow me

to have confidence in any primary efficacy result of this study, even if the ostensible p value reported by the sponsor was < 0.05.

(b) (4)

- I am concerned about the relatively small number of patients studied in the randomized, placebo-controlled study phase (19 patients/treatment group of lamotrigine or placebo) which does not seem to facilitate the collection of robust/reliable data.

(b) (4)

(b) (4)

[redacted]

1.3.3 Safety

Reviewer Safety Conclusions

- I conclude that there are 3 major problems/concerns with the regard to the safety data (b) (4) [redacted] (see section 7 Integrated Review of Safety and section 7.1 Methods and Findings).

    - The small number of randomized patients (19/treatment group) and study design (randomized withdrawal) in the relatively brief (up to 8 weeks, and frequently much less for many patients) placebo-controlled study phase and short did not facilitate collection of useful safety data.

    - The sponsor did not adequately collect adverse event data that might reflect adverse reactions related to symptoms which were not able to be communicated in this very young population.

    - The sponsor's coding and analyses of adverse events appeared to be of poor quality and did not seem to provide a reliable assessment of not only the frequency of certain adverse event safety data but also the nature/type of certain adverse events.

- There were no placebo-controlled safety data collected during the titration phase. Treatment during the titration phase is frequently not only associated with the development of many adverse events but also adverse events of greater frequency and possibly even greater severity than adverse events that can develop in the maintenance period after maximal lamotrigine titration has occurred and the patient had demonstrated tolerability.

- The vast majority of safety data collected resulted from open-label treatment which typically significantly underestimates the frequency of adverse events. Long-term, open-label data are particularly helpful in characterizing more uncommon or rare adverse reactions to treatment and do not substitute for placebo-controlled safety data.

- The absence of placebo-controlled safety data during the lamotrigine titration phase in an unselected population did not allow one to characterize the basic safety profile of lamotrigine for this young population. Comparison of placebo-controlled safety data (i.e.

placebo vs drug treatment) is the main method by which we assess the basic safety profile of a drug for treatment of a certain, unselected population.

- There was no attempt to characterize dose-response (b) (4) [redacted] There was no attempt/consideration to characterize dose-response by randomizing patients to more than one fixed lamotrigine dose. (b) (4) [redacted]

- The sponsor did not provide any adverse event analyses during the titration vs the maintenance phases in the open-label experience. Such analyses might show an increased frequency of adverse events developing during the titration phase.

- The safety data collected during the randomized, withdrawal placebo-controlled phase seems to be of limited value because this brief treatment phase (ranging from a few days to a maximum of 8 weeks) captures safety data after patients have been treated with a tolerable lamotrigine dose and frequently have already experienced adverse events previously while being titrated and maintained on a seemingly therapeutic and tolerable lamotrigine dose.

- There was no collection of blood pressure data in this very young population. Lamotrigine has the potential (as does any CNS acting drug) to alter blood pressure (especially lower blood pressure). Given this possibility and that the significant frequency of "dizziness" (which I do not think can exclude a decrease in blood pressure in at least some lamotrigine treated patients) observed in older pediatric patients (and adults), it is conceivable that lamotrigine could be exerting significant effects on blood pressure, an important vital sign parameter that was not collected (for unknown reasons). Although the lamotrigine label does not describe effects on blood pressure, I am not confident that data have been adequately collected and analyzed to demonstrate or exclude effects on blood pressure (especially related to changes of position and time of dosing). I cannot think of a good reason why blood pressure was not measured and collected throughout these studies. Furthermore, normative data exist for this very young population.

(b) (4) [redacted]

(b) (4)

1.3.4 Dosing Regimen and Administration

- Not applicable (b) (4)

1.3.5 Drug-Drug Interactions

- Not applicable (b) (4)

1.3.6 Special Populations

- Not applicable (b) (4)

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

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

2.2 Currently Available Treatment for Indications

[redacted]^(b) (4)

chronic administration of AEDs is the most common means of treating epilepsy in infants. Carbamazepine, phenytoin, and phenobarbital are the most commonly prescribed treatments. Valproic acid (VPA) is also used in pediatric subjects despite the need for close scrutiny of laboratory values due to the high incidence of hepatic failure in infants.

GlaxoSmithKline (GSK)-sponsored clinical trials to date that have evaluated lamotrigine for treatment of epilepsy have been limited to subjects 2 years of age and older. In addition, there is little published information on the pharmacokinetics, safety or efficacy of lamotrigine in subjects less than 2 years of age. LAM20006 provides information on the effectiveness of LAMICTAL in the very young as well as additional dosing information in the setting of a responder-enriched clinical trial. Open-label study LAM20007 was required to assess the long-term safety and tolerability of lamotrigine therapy.

2.3 Availability of [redacted]^(b) (4) Active Ingredient in the United States

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

2.4 Important Issues With Pharmacologically Related Products

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

2.5 Presubmission Regulatory Activity

The FDA, pursuant to the Section 505A of the Federal Food, Drug and Cosmetic Act, issued the formal Written Request for LAMICTAL on 17 December 1998 in response to a Proposed Pediatric Study Request submitted by GlaxoSmithKline (GSK) on 3 August 1998 to the NDA 20-764 for LAMICTAL (lamotrigine) Chewable Dispersible Tablets.

The original Written Request was amended on 3 July 2000, 21 December 2001 and 10 May 2004. An overview of the request and matching study information is given in the annotated Written Request and a detailed chronology of correspondence is provided in Studies LAM20006 and LAM20007 respond in full to the Written Request and its amendments.

Chronology of Interactions with FDA Regarding Written Request for Pediatric Studies
Date Summary of Interaction

- August 3, 1998 Initial submission of Proposed Written Request based on completed, but unsubmitted study evaluating LAMICTAL in pediatric patients age **2-16 years** with partial seizures (US40). GSK requested that this study form basis of Written Request

- December 17, 1998 FDA issues Written Request comprising the following: placebo-controlled study of safety and efficacy as adjunctive treatment of partial seizures, pharmacokinetic information, and long-term safety in pediatric patients age **1 month to 16 years** of age

- February 9, 1999 GSK proposes Modified Written Request to evaluate PK and long-term safety only in patients age 1 month to 2 years. GSK position was that controlled efficacy study in 1 month to 2 years was not needed if PK data were obtained (could extrapolate to older patients) and would not be feasible due to complexity of lamotrigine/LAMICTAL dosing and ethics of doing controlled study in this age group. Requested that efficacy study be limited to ages 2-16 years (which was already met by completion of Study US40, submitted as part of NDA 20-241/S-008 and NAD 20-764/S-002 on January 28, 1999 and approved on January 17, 2003). In this correspondence, GlaxoSmithKline agreed to conduct the safety and pharmacokinetic study as outlined in the Written Request.

- March 29, 1999 Teleconference with FDA (b) (4)

- September 24, 1999 Submission of meeting request to discuss proposed design for

efficacy study in patients age 1 month to 2 years, proposal for partial waiver for 2-16 years of age due to pending sNDA seeking approval of LAMICTAL for adjunctive treatment of partial seizures in patients age 2-16 years (US40 was pivotal study). Meeting was granted for November 10, 1999.

- November 10, 1999,
  January 13, 2000,
  February 25, 2000
  Submissions and teleconferences to reach final agreement on Written Request, study design, issuance of Modified Written Request

- April 19, 2000/April 26, 2000 Submission of protocols LAM20006 (controlled efficacy and PK study) and LAM20007 (long-term extension study) to IND 43,551 (Serial No.0147 and 0149, respectively

- July 3, 2000 FDA Issues Modified Written Request comprising controlled study of adjunctive treatment of partial seizures, PK information, and long-term safety in patients age 1 month to 2 years of age. Study 1 should establish the efficacy, short-term safety, and pharmacokinetic of lamotrigine, (open-label lead in phase, followed by a double-blind, placebo-controlled, randomized, add-on phase assessing the efficacy and safety and pharmacokinetics) study 2 should determine the long-term safety of lamotrigine((open, uncontrolled, long-term). Latest submission date for consideration for exclusivity **August 24, 2003**

- March 16, 2001 Submission of meeting request (serial number 0170) to discuss decreasing sample size of LAM20006 (from 60 patients to 38 patients) due to observed difference in dropout rate seen in conduct of study vs previously assumed dropout rate used to determine sample size and to obtain FDA's comment on proposals to amend the protocols to : 1) allow US patients receiving vigabatrin to be eligible for the study; 2) allow patients receiving additional short-term antiepileptic drugs (AEDs) in the Open Label Phase to be eligible for the stud (b) (4)

- May 10, 2001 Teleconference with FDA to discuss March 16, 2001 proposal. FDA had no objection to allow patients receiving vigabatrin to enter the study or to allow the short-term addition of AEDs during the open-label phase of LAM20006. (b) (4)
  GlaxoSmithKline meeting minutes were submitted on June 14, 2001 (serial number 0177).

- August 28, 2001 Submission of draft protocol amendment (serial number 0181) which provided a revised sample size estimate of 19 subjects per treatment group and requested

a change to the Modified Written Request from July 3, 2000 to extend the deadline for submission from August 24, 2003 to December 1, 2006. In a teleconference on October 24, 2001 the Agency accepted the proposal to reduce the sample size and the extended timeline.

- October 24, 2001 Teleconference with FDA to discuss August 28, 2001 proposal. FDA agreed in principle to decreased sample size but cautioned that sample size needs to be large enough to detect a difference if one exists. Also agreed to extension of submission of final reports.

- December 21, 2001 Issuance of Modified Written Request with new due date of **December 1, 2006.**

- May 10, 2004 Amendment to the Written Request specifying the format of reports to be submitted section regarding categorization of pediatric patients included in the studies for race and ethnicity.

The sponsor did not have a Pre-NDA meeting with the DNP to plan this NDA submission. I believe that the last contact with the DNP regarding any meeting (face to face or teleconference) was the last 2001 teleconference discussing the amendment to allow patients in the randomized phase with a > 80 % "response."

2.6 Other Relevant Background Information

There is no other information relevant here.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There is no other information relevant here with the exception of the following information contained in the question-based Clinical Pharmacology review.

(b) (4)

3.2 Animal Pharmacology/Toxicology

There is no other information relevant here because no specific information data was submitted regarding animal pharmacology/toxicology..

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All document reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

\\Cdsesub1\n20241\S_032\

4.2 Tables of Clinical Studies

Table 3 Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects, Gender M/F (number of subjects), Mean Age (range), Race (number of subjects)	Study Reporting Status (Type of Report)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
LAM20006 (RM2003/00539/00, m5.3.5.1.)	Compare efficacy of LAMICTAL add-on therapy to placebo, safety, PK	DB, PC, R, responder-enriched	Pediatric patients 1-24 months of age with uncontrolled partial seizures	LAMICTAL chewable/dispersible tablets and matching Placebo tablets, three times daily, oral, add-on therapy; maximum maintenance dose of 5.1 mg/kg/day for subjects on VPA or non-EIAEDs and 15.6mg/kg/day for subjects on EIAEDs; 38 weeks maximum	177 (OLP) 38 (DBP), 92 Male 85 Female, 13.0 months (1-24), White 149 Black 13 Asian 2 American Hispanic 9 Other 4	Completed (CSR)
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
LAM20007 (RM2006/00088/00, m5.3.5.2)	Long-term safety, efficacy, PK, continuation study	OL, UC	Pediatric patients previously enrolled in LAM20006 or LAMICTAL-naïve patients 1-24 months of age with uncontrolled partial seizures	LAMICTAL chewable/dispersible tablets, three times daily, oral, add-on therapy; maximum maintenance dose 5.1 to 10.2mg/kg/day for subjects on VPA or non-EIAEDs and 15.6 to 30mg/kg/day for subjects on EIAEDs; 48 weeks or until second birthday (whichever occurred later)	206, 114 Male 90 Female, 15.9 months (2-32), White 171 Black 9 Asian 2 American Hispanic 14 Other 8	Ongoing (interim aCSR)

4.3 Review Strategy

My review strategy was to review results of each study (20006 including open-label phase and randomized, double-blinded, placebo-controlled study phase of 20006 and 20007) separately but also to look at safety results combined from both studies.

4.4 Data Quality and Integrity

Dr. Gucuyener's site was selected for inspection because there were insufficient domestic data and this site had the largest enrollment for the studies 20006 (including the randomized, double-blind, placebo-controlled study phase) and 20007 . The goals of the inspection were to assess adherence to FDA regulatory requirements: specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

The following was abstracted from the Division of Scientific Investigation (DSI) report :

Observations noted below are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

A. Protocol # LAM 20006
1. Kivilcim Gucuyener, M.D. , Site # 022200
Gazi Universitesi Tip Fakultesi
Pediatrik Noroloji Bilim Dali
Kat:10 Besevler
Ankara 06500
Turkey

a. What was inspected: Dr. Gucuyener enrolled 10 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.
b. Limitations of inspection: None
c. General observations/commentary: No significant regulatory violations were noted.
d. Data appear acceptable.
B. Protocol # LAM 20007
1. Kivilcim Gucuyener, MD Site # 022200
Gazi Universitesi Tip Fakultesi
Pediatrik Noroloji Bilim Dali
Kat:10 Besevler
Ankara 06500
Turkey
a. What was inspected: Dr. Gucuyener enrolled 15 subjects. The inspection encompassed an audit of all
subjects' records. Primary endpoint efficacy data were verified for all subjects.
b. Limitations of inspection: None
c. General observations/commentary: No significant regulatory violations were noted.
d. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS
As mentioned above, the inspection of Dr. Gucuyener found no significant deviations from FDA

regulations. The data from this site appear acceptable in support of the respective indication. As previously mentioned, observations noted above are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Reviewer Comment

- Inspection of this single most important site for both studies (and especially the randomized, double-blind, placebo-controlled study phase) did not suggest any significant concerns.

4.5 Compliance with Good Clinical Practices

Reviewer Comment

- I did not find anything to suggest that the studies were not conducted with regard to Good Clinical Practices.

4.6 Financial Disclosures

Reviewer Comment

- There did not appear to be any financial disclosure information that suggested any potential concerns.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following information and conclusions were abstracted from the Clinical Pharmacology Review by Drs. Sally Yasuda and Rajnikanth Madabushi.

Traditional pharmacokinetic (PK) data from Week 5 in Study LAM20006 are shown in Table 4.

Table 4 Week 5 PK Data in LAM20006 in Subjects with 8 hour dosing interval

	Enzyme Inducers (n=23) (Dose range 2-17 mg)	**Valproic Acid** (n=8) (Dose Range 2-5 mg)	**Neutral** (n=2) (Dose Range 2 mg only)
Tmax (hrs)	2.0 (0-8)	1.83 (0-6)	4.0 (2-6)
Cmax (µg/ml)	1.25 (42)	2.21 (61)	0.26 (73)
AUC0-8 (µg*hr/ml)	7.38 (37)	16.88 (66)	1.775 (70)
Clss/F (l/hr)	1.34 (37)	0.24 (47)	1.50 (70)
Clss/F (ml/min/kg)	2.44 (41) (range: 1.08-5.21)	0.35 (49) (range: 0.155-0.613)	2.82 (76) (range: 1.26-4.39)
% Degree of fluctuation, mean	66 (n=21)	8	38%
% Swing, mean	105 (n=21)	8	48 %
Weight (kg)	9.3 (20%)	11.8 (14%)	9.3 (11%)

Generally similar results were observed in traditional PK evaluated in Study LAM 20007. In both cases, there were very few subjects in the groups taking concomitant "neutral" AEDs (or concomitant Valproic Acid" in the case of LAM 20007). However, the results suggest that subjects taking concomitant "neutral" AEDs or enzyme inducing AEDs (EIAEDs) have faster clearance than the subjects taking valproic acid. (b) (4)

(b) (4)

(b) (4)

PK Conclusions

• A one-compartment open model with 1st order absorption and elimination adequately describes the serum concentration time profile of lamotrigine in pediatric patients aged 2.4 – 25.8 months.

• Concomitant AEDs (Inducers and VPA) and body weight were found to be the major explanatory variables for the inter-individual variability associated with oral clearance of lamotrigine.

• The oral clearance of lamotrigine is increased by 80% when administered with glucuronidation inducing AEDs such as Phenytoin, Carbamazapine, Phenobarbital, etc.

• The oral clearance of lamotrigine is decreased by 70% when administered with VPA.

• Bodyweight accounts for the age-related effects on the oral clearance of lamotrigine.

• Increasing exposures in open label phase result in greater reduction of seizure frequency compared to historical baseline. However, time and drug effect are confounded in the present exploratory analysis.

• The significant limitations (e.g. number of subjects) in the traditional PK data set do not allow for conclusions to be drawn regarding comparisons between the different classes of concomitant AED. However, as previously observed in other studies, the apparent oral clearance appears to be lower in the valproic acid and neutral groups than in the enzyme inducer group at 5 weeks.

• The mean average total daily lamotrigine dose for the neutral group was approximately 19% greater than that of the valproic acid group.

5.2 Pharmacodynamics

The sponsor did not provide specific information about pharmacodynamics nor analyses of exposure-response relationships.

The following information about pharmacodynamic effects is abstracted from the lamotrigine label.

Mechanism of Action : The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of this animal model to specific types of human epilepsy is unclear.

The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have not been established.

Pharmacological Properties : Although the relevance for human use is unknown, the following data characterize the performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT $_3$ receptor (IC $_{50}$ = 18 muM). It does not exhibit high affinity binding (IC $_{50}$ >100 muM) to the following neurotransmitter receptors: adenosine A $_1$ and A $_2$; adrenergic alpha $_1$, alpha $_2$, and beta; dopamine D $_1$ and D $_2$; gamma-aminobutyric acid (GABA) A and B; histamine H $_1$; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT $_2$. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC $_{50}$ = 145 muM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC $_{50}$ >200 muM) when tested in rat synaptosomes and/or human platelets in vitro.

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity :
Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC $_{50}$ for lamotrigine effects on NMDA-induced currents (in the presence of 3 muM of glycine) in cultured hippocampal neurons exceeded 100 muM.

Folate Metabolism : In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and

maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys: Lamotrigine was found to accumulate in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to alpha-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

5.3 Exposure-Response Relationships

The sponsor did not conduct and submit analyses regarding exposure-response relationships. However, the pharmacometric reviewer, Dr. Madabushi, conducted some preliminary and exploratory analyses which suggest the possibility exposure-response relationships might exist (see PK Conclusions of section 5.1 Pharmacokinetics).

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

(b) (4)

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6.1.1 Methods

The sponsor conducted a single, small randomized, double-blind, placebo-controlled withdrawal study to investigate efficacy.

Efficacy data were collected on all subjects who participated in the OLP of the study. Daily counts of each seizure type, duration of innumerable seizure episodes, and absence of seizure activity were recorded in the seizure diary and the diary was collected at each scheduled visit to the study site. Site personnel thoroughly reviewed the diary with the

parent/caregiver at each study visit. Diary entries were to be unambiguous and legible; any corrections made by the caregiver or site personnel were initialed and dated. Site personnel transcribed the seizure data into the CRF with the diary pages serving as source documentation.

6.1.2 General Discussion of Endpoints

The sponsor proposed that the primary efficacy endpoint for the randomized, double-blind, placebo-controlled study phase of study 20006 would be the proportion of patients who were treatment failure during the randomized phase. Treatment failure was defined as having one or more escape criteria.

Individual efficacy escape criteria were defined as follows:

- 50% or greater increase in monthly partial seizure frequency compared to the frequency of seizures during the Optimization Period. Monthly seizure frequency was computed using the last 4 weeks of the optimization period and the most recent 4 weeks of the DBP. If a subject had not reached 4 weeks in the DBP but had already experienced a total number of seizures =150% of the seizures of the Optimization Period, the subject was considered to have met the escape criterion;
- Doubling of the highest consecutive 2-day partial seizure count observed during the Optimization Period;
- Onset of a new and more severe seizure type;
- Clinically significant worsening of non-partial seizures observed during the Historical Baseline Phase or the Optimization Period;
- The need to use any therapeutic intervention to control seizures; or
- Status epilepticus.

Reviewer Comments

I have some concerns about the relevance or appropriateness two of these escape criteria (b) (4)

- It is not clear to me that clinically significant worsening of non-partial seizures should impact on assessing or determining the effect of treatment for partial seizures.

- Neither is it clear that the use of any therapeutic intervention to control seizures is an appropriate escape criterion particularly if the intervention is prompted to control non-partial seizures. Applying this medical intervention as an escape criterion/reason did not require that the intervention necessarily be directed toward controlling partial seizures. Patients who had other seizure disorders (including primary generalized seizures and other seizure disorders) were allowed to enroll in the trial. Thus, the results of this study were potentially confounded by the possibility that seizures unrelated to partial epilepsy

could have caused caused a patient to "escape" and be considered a treatment failure and impact on the determination of lamotrigine efficacy for treatment of partial seizures.

- It appears that one patient (#5983) in the placebo group was classified as a treatment failure based upon one (clinical worsening of non-partial seizures) of these 2 questionable criteria along with the criterion of onset of new and worse seizure. Considering that the latter criterion was also met, the clinical worsening of non-partial seizure does not seem to be a problem. However, another patient (# 6480, treated with lamotrigine) was classified as a treatment failure based upon the need for medical intervention. I do not believe that any other patients were classified as a treatment failure based upon either or both of these 2 questionable criteria.

6.1.3 Study Design

Primary efficacy endpoint(s)
The primary efficacy endpoint was the proportion of subjects receiving LTG versus placebo meeting the escape criteria during the DBP of the study.

Secondary efficacy endpoint(s)
Secondary efficacy endpoints included the following:
· The difference in the time to escape patterns between subjects receiving LTG and placebo.
· The proportion of subjects achieving a reduction in monthly partial seizure frequency from baseline of ≥40% at the end of the OLP.
· Percent change from baseline in seizure frequency at the end of the OLP by seizure type.
· The investigators' global evaluation of the subjects' status at the end of the OLP and DBP.

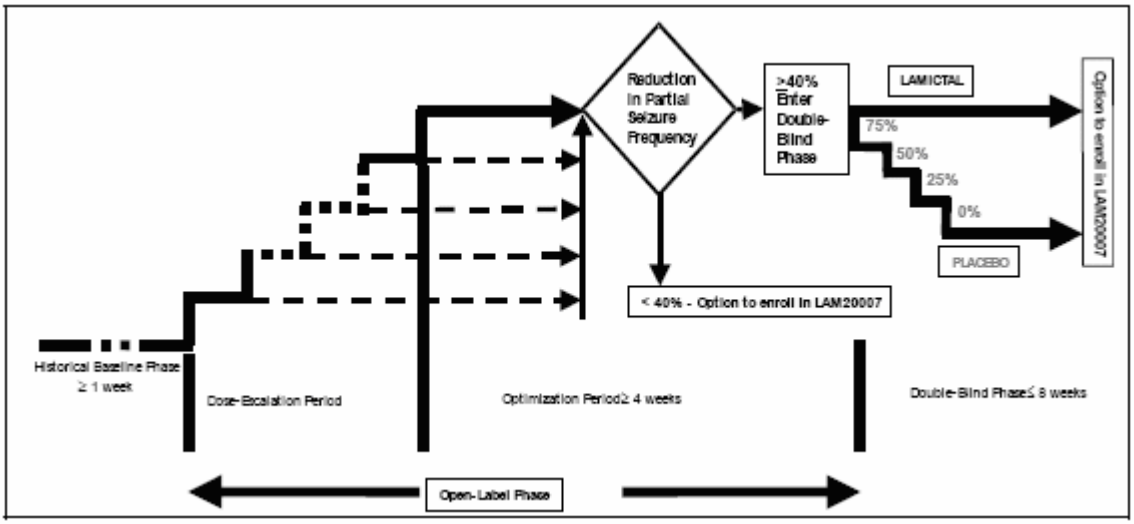
Study Rationale
GSK-sponsored clinical trials to date that have evaluated LTG for treatment of epilepsy have been limited to subjects 2 years of age and older. In addition, there is little published information on the pharmacokinetics, safety or efficacy in subjects less than 2 years of age. This study will provide information on the effectiveness of LTG in the very young as well as additional dosing information in the setting of a well-controlled clinical trial.

Study Objectives
The primary objective of this study was:
· To compare the efficacy of LAMICTAL as add-on therapy versus placebo in subjects 1 to 24 months of age with partial seizures.
The secondary objectives of this study were:
· To assess the safety of LAMICTAL as add-on therapy in subjects 1 to 24 months of age with partial seizures, and,

· To determine the pharmacokinetics of LTG in this age group.

This was an international, multi-center study consisting of an open-label period followed by a parallel, randomized, double-blind, placebo-controlled period Figure 1. Male or female pediatric subjects (1-24 months of age) diagnosed with epilepsy whose partial seizures were uncontrolled by one or more marketed AEDs were eligible for entry into the open-label, uncontrolled phase of the study. Although subjects may have had multiple types of seizures at enrollment, at least four reliably detectable partial seizures per month (extrapolated from a ≥1 week historical observation period) were required in order to be eligible for enrollment.

Figure 1 Safety, Pharmacokinetics, and Efficacy of Add-on LAMICTAL in Pediatric Age Subjects (1-24 months) with Partial Seizures (LAM20006)



After written informed consent was obtained, male or female subjects were screened to assess eligibility criteria (e.g., at least 4 partial seizures per month based on a ≥1 week historical baseline period). Lamotrigine (LTG) was started as an add-on therapy during an Open-Label Phase (OLP). One or two background AEDs were allowed; however, VPA had to be given alone. Subjects who were receiving three AEDs (other than VPA) were allowed to enter the study if one of the AEDs was tapered during lamotrigine titration in the OLP. At the end of Week 2, a blood sample was collected to determine the LTG serum concentration and adjustments to dose escalation, if necessary. Pharmacokinetic samples were collected from consenting subjects at approximately the end of Week 5 or 6. A blood sample was collected at the end of the OLP for determination of the presence of the 583C80 metabolite. During the OLP, investigators titrated the dose of lamotrigine until, in their opinion, optimal clinical benefit (maximum seizure control and minimum adverse experiences) had been achieved. The period of optimal clinical benefit, or optimization, had to be maintained for at least 4 weeks (i.e., 28 days) during which there could be no changes to the background AEDs. Additionally, lamotrigine doses were to remain unchanged during the last 2 weeks of the optimization period. Subjects achieving a ≥ 40% reduction from baseline in partial seizure frequency during the last 28 days of

the optimization period, when compared to baseline, were randomized (1:1) to either continued LTG treatment or a gradual, blinded withdrawal of LTG to placebo. Subjects remained in the Double-Blind Phase (DBP) of the study for 8 weeks or until one of the escape criteria was met.

Initially, the criterion for randomization was a reduction in seizure $\geq$ 40 % and up to 80 %. However, because enrollment was going slowly because many patients had a "response" > 80 %, the sponsor amended the protocol to allow any response $\geq$ 40 % seizure rate reduction.

The schedule of study events and their timing is displayed in Table 7 for the OLP and in Table 8 for the DBP.

Table 7 OL-Lead-In Phase Time and Schedule of Events

Study Phase	Screen	Week of Dosing[a]														Follow-up[b]
		2	4	5	6	8	10	12	14	16	18	20	22	24[c]	26[c]	EOP[d]	
Informed Consent	x																
Inclusion/Exclusion	x																
Demographics	x																
Current Medical Condition	x																
Vital Signs	x	x	x		x	x	x	x	x	x	x	x	x	x	x		x
Neuro. Exam	x	x	x		x	x	x	x	x	x	x	x	x	x	x		x
Seizure Count	x[e]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Hem./Chem. Labs	x					x										x	x
ECG	x					x										x	x
Daily Diaries	Throughout the Study																
Dispense Study Medications	x	x	x		x	x	x	x	x	x	x	x	x	x	x		
PK Samples[f]				x													
Plasma Sample		x														x[g]	
Adverse Events		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Investigator's Assessment of Clinical Status		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

a Optimization may be reached before Week 22 (for subjects on background EIAEDs) or Week 26 (for subjects on background VPA).
b For subjects who discontinue the study during the open-label phase and who do not enroll in LAM20007 or switch to marketed LAMICTAL. Follow-up visits should be scheduled 1 week after the last dose of open-label LAMICTAL has been taken.
c For subjects on background VPA only
d End Of Phase. For subjects who have completed the optimization period or have completed the open-label phase without achieving optimization.
e Seizure history
f Pharmacokinetic samples to be collected from consenting subjects at selected sites at approximately the end of Week 5 (for subjects receiving an EIAED) or at the end of Week 6 (for subjects receiving a non-EIAED or VPA). Blood (1mL) and saliva samples (0.5-1mL) for determination of lamotrigine concentrations to be collected before dose and at 1, 2, 3, 4, 6, and 8 hours after dose. For subjects where it is not possible to obtain all of the blood samples, saliva samples should be collected at all the time points and blood samples may be obtained at only pre-dose, 2, and 6 hours post dose.
g Collect a plasma sample for lamotrigine metabolite (583C80) at last open-label visit.

Table 8 Randomized, double-blind, placebo-controlled study phase Time and Schedule of Events

Study Phase: Randomization[a]	Week of Dosing[b]				Final Visit	Follow-up[c]
	2	4	6	8		
Vital Signs	x	x	x	x		x
Phys./Neuro. Exam	x	x	x	x		x
Hem./Chem. Labs					x	x
ECG					x	x
Daily Diaries	Throughout the Study					
Dispense Study Medications	x	x	x	x		
Adverse Events	x	x	x	x	x	x
Investigator's Assessment of Clinical Status	x	x	x	x	x	x
End of Study Record						x

a. For subjects who optimize with ≥40% decrease in seizure frequency during open-label phase.
b. During double-blind phase
c. For subjects who discontinue the study and who do not enroll in LAM20007. Follow-up visits should be scheduled 1 week after the last dose of study drug has been taken.

Discussion of Study Design, Including the Choice of Control Group(s)
The following is the sponsor's discussion of study design and choice of control groups.

This study used a responder-enriched design in which all subjects first received open-label LTG. In this design, only subjects who achieved a defined level of response during the OLP phase were eligible for entry into the DBP. During the DBP, subjects were randomized to either continue their optimized dose of LTG or gradually withdraw the dose of LTG using a matching placebo to maintain the blind. This design was chosen to provide an adequate and well-controlled evaluation of the efficacy of LTG in infants while minimizing their exposure to placebo. Subjects randomized to withdrawal of LTG continued to receive their background AED(s). Presence of background AED(s) plus the use of pre-defined escape criteria offered a measure of protection for the subjects. Repeated blood sampling in this age group presented technical difficulties that limited the number of samples that could be obtained per subject as well as the number of subjects who would volunteer to participate. An alternative approach was the use of saliva instead of blood for monitoring plasma levels of AED. This has been demonstrated to be a useful approach in a clinical setting with many, but not all AEDs showing highly significant correlations between plasma and saliva AED levels. In addition, saliva sampling was greatly preferred over blood sampling by parents of children that are receiving AEDs. Studies were performed that examined the relationship between plasma and saliva levels of LTG in adults. Robust correlations (r=0.89-0.96) were observed with saliva levels being approximately 60% of the plasma concentrations.

Inclusion Criteria :
A subject was eligible for inclusion in this study only if all of the following criteria applied:
1. Had a confident diagnosis of epilepsy.
2. Had a history of ≥4 reliably detectable recurrent partial seizures (simple, complex, or those that evolve to secondarily generalized seizures) per month preceding entry into

the protocol.
3. Was a male or female pediatric subject between the ages of 1 and 24 months at the time of study entry. Minimum age of 1 month was based on a 44-week conceptional age.
4. Subjects on non-EIAEDs (including VPA) weighed at least 6.7kg at study entry.
5. Had seizures uncontrolled by at least one other AED whose plasma concentrations were within the acceptable ranges for therapy.
6. Had laboratory and hematology values at screening, which would be considered within normal limits, or not clinically significantly abnormal, for age, weight, and medical condition.
7. Had no underlying chronic metabolic abnormalities (e.g., phenylketonuria) which could confound or cause seizure activity.
8. Had a parent/caregiver who was capable and willing to maintain a complete and accurate record of seizures.
9. Had a 12-lead ECG with PR, QRS, QT, and QTc intervals within normal limits for age.
10. Had a parent/caregiver that provided written informed consent prior to study participation.

Exclusion Criteria :
A subject was **not** eligible for inclusion in this study if any of the following criteria applied:
1. Had a diagnosis of severe, progressive myoclonus.
2. Had seizures not related to epilepsy (e.g., related to hypoglycemia, hypocalcemia or hypomagnesemia, sepsis, drug intoxication (theophylline, local anesthetics) or pyridoxine dependency.
3. Had seizures as a result of drug withdrawal (maternal abuse of drugs).
4. Had previously demonstrated a sensitivity or allergic reaction to LAMICTAL or related compounds.
5. Had a pre-existing medical condition likely to interfere with the completion of the study. (e.g., Status epilepticus within 4 weeks of enrollment)
6. Had a caregiver unable or unwilling to observe the subject and complete the required medical diary.
7. Had a progressive or unstable neurologic condition with evidence of deterioration within the last month.
8. Had taken any experimental medication within the last 30 days prior to screen assessments (or five half-lives, whichever is longer; with the exception of vigabatrin in the US, as per Amendment 05).
9. Had any clinically significant chronic cardiac, renal, hepatic, or gastrointestinal condition, which may affect the absorption, distribution, metabolism or elimination of drugs.
10. Had previously been treated with LTG.
11. Was on a maintenance regimen of more than two background AEDs.
12. Was taking VPA with one or more additional AEDs.
13. Had taken VPA for <6 months or >6 months and had evidence of hepatic

dysfunction.
14. Was on ketogenic diet.
15. Was currently taking felbamate.
16. Was currently taking adrenocorticotropic hormone (ACTH), as per Amendment 2.
17. Had a surgically implanted and functioning Vagus Nerve Stimulator (VNS), as per Amendment 2.

Dose Rationale
The dosing regimens for LTG used in this study were the same on a mg/kg basis as those recommended for pediatric subjects aged 2 to 16 years. These regimens were established using a population pharmacokinetic model and were selected to ensure that the serum concentrations of LTG observed during dose escalation increased in a similar fashion in pediatric and adult subjects. Since LTG clearance in pediatric subjects is inversely related to body weight, the recommended doses, which are the same mg/kg across all weights, represent a compromise. For lower weight subjects, particularly those under 10kg, the dose escalation regimens result in serum concentrations lower than those predicted in adult subjects. Thus in terms of the expected rate of increase in LTG concentration, the recommended doses are increasingly conservative at lower body weights.

Treatment Assignment
Subjects were assigned to study treatment in accordance with a central randomization procedure. Subjects achieving a ≥40% (≥40% to ≤80% prior to amendment 6) reduction in partial seizure frequency over the last 4 weeks of the OLP compared to the Historical Baseline Phase were randomized to either placebo or continued LTG treatment in a 1:1 ratio. Subsequently, a protocol amendment allowed any patients with ≥ 40 % "response" to be randomized.

6.1.4 Efficacy Findings

Disposition of Subjects

A total of 177 subjects from 14 countries were enrolled in the OLP. One hundred thirty-nine (139) subjects prematurely discontinued the OLP phase. The majority of those subjects (80/139) failed to meet the criteria for randomization to double-blind treatment.

Thirty eight (38) subjects were randomized to the DBP of the study (19 in each treatment group). Two subjects in the Lamotrigine group were prematurely discontinued from the DBP without meeting escape criteria due to protocol violations. Seventeen subjects in the Lamotrigine group and 19 subjects in the placebo group completed the DBP of the study. Two additional subjects were excluded from the ITT patient population due to protocol violation, resulting 17 subjects in each treatment groups in the per-protocol patient population.

Demographic Characteristics

Key demographic characteristics for the OLP Population and by treatment randomization for the ITT – DBP Population are summarized below in Table 9 and Table 10 . **Note that only one subject was in the < 6 months age group and this patient was randomized to placebo group.**

Table 9 Summary of Key Baseline Characteristics (Source: Table 10 of Study Report)

Baseline Characteristic	OLP LAMICTAL (N=177)	ITT – DBP (N=38)	
		Placebo (N=19)	LAMICTAL (N=19)
Age at First Seizure (Months)			
Median	3.0	3.0	3.0
Range	0 – 20	0 - 12	0 – 15
Duration of Epilepsy (Months)			
Median	7.36	8.53	9.14
Range	0.4 – 23.5	1.0 – 22.7	3.4 – 21.8
Presenting Seizure Types			
Simple Partial Seizures	42 (24%)	4 (21%)	8 (42%)
Complex Partial Seizures	118 (67%)	16 (84%)	10 (53%)
Sec. Generalized Seizures	77 (44%)	6 (32%)	7 (37%)
Generalized Seizures	46 (26%)	6 (32%)	5 (26%)
Seizure Etiology			
Idiopathic	70 (40%)	8 (42%)	3 (16%)
Symptomatic	105 (59%)	11 (58%)	16 (84%)
Missing	2 (1%)	0	0
Concomitant AED Group			
Induced	126 (71%)	14 (74%)	13 (68%)
Non-induced	51 (29%)	5 (26%)	6 (32%)

Source Data: Table 12.5
1. Induced = Enzyme inducing AEDs (EIAED), Non-induced = Non-enzyme inducing AEDs (including VPA alone).

Table 10 Demographic Characteristics - Safety Population (Source: Table 9 of Study Report)

Demographic Characteristic	OLP LAMICTAL (N=177)	ITT – DBP (N=38)	
		Placebo (N=19)	LAMICTAL (N=19)
Gender - n (%)			
Male	92 (52%)	9 (47%)	12 (63%)
Female	85 (48%)	10 (53%)	7 (37%)
Age (months)			
Median	13.17	14.16	13.54
Range	1.0 – 24.0	2.0 - 23.3	6.6 – 23.9
Age group (months)			
<6	28 (16%)	1 (5%)	0
≥6 - ≤12	56 (32%)	6 (32%)	8 (42%)
>12	93 (53%)	12 (63%)	11 (58%)
Race - n (%)			
White	149 (84%)	17 (89%)	17 (89%)
Black	13 (7%)	0	0
American Hispanic	9 (5%)	2 (11%)	1 (5%)
Asian	2 (1%)	0	0
Other	4 (2%)	0	1 (5%)
Weight (kg)			
Median	9.60	10.10	10.00
Range	2.9 – 17.3	4.5 - 13.2	7.1 – 17.3

Source Data: Table 12.4

Primary Efficacy Results

The primary efficacy endpoint was the proportion of lamotrigine versus placebo subjects meeting the escape criteria during the DBP of the study. The proportion of subjects who escaped (i.e., treatment failures) during the double blind phase of the study is shown below in Table 11 for the primary modified ITT analysis (including counting patients as treatment failure who discontinued prematurely but not for an adverse event) and the Per Protocol analysis.

Table 11 Proportion of subjects who met escape criteria during the DBP (LAM20006)

	Placebo		LAMICTAL		
Analysis Population	N	Treatment Failures	N	Treatment Failures	p-value[1]
ITT DBP[2]	19	16 (84%)	19	11 (58%)	0.074; 0.151
PP DBP	17	14 (82%)	17	9 (53%)	0.067; 0.141

Source data: Table 13.1

1. p-values: two tailed chi-square test and Fisher's exact test, respectively
2. Two LAMICTAL subjects who did not meet escape criteria but discontinued prematurely were counted as treatment failures in the ITT DBP analysis.

The proportion of treatment failures was greater among subjects receiving placebo (84% and 82% for the ITT DBP and PP-DBP populations, respectively) compared with those receiving lamotrigine (58% and 53%, respectively). The difference between treatment groups approached, but did not achieve, statistical significance. The ITT/Worst case DBP analysis was identical to that of the ITT DPB analysis. Of the pre-defined escape criterion, a ≥50% increase in monthly partial seizure frequency was most frequently met either alone or

with other criteria and accounted for 81% (13/16) of escapes in the placebo group and 67% (6/9) of escapes in the lamotrigine group in the ITT DBP population.

Protocol Violators
Two patients in the lamotrigine (# 6333 and # 6336) and placebo (# 6229 and # 6372) treatment groups were considered protocol violators.

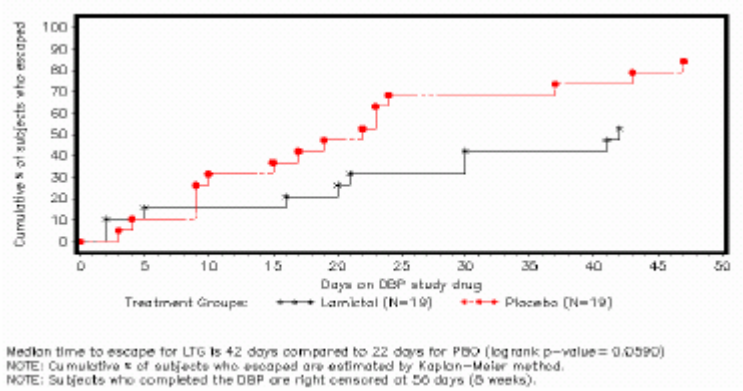
There were 2 lamotrigine group subjects (patient number 6333 and 6336) who discontinued prematurely for reason of protocol violation. The sponsor originally told the Agency that the two patients did not meet the escape criteria at the time of discontinuation. During the course of review, we asked sponsor through emails for specific reasons of protocol violation with regard to these two patients, which were not described in the submission. The sponsor later responded that patient 6336 had actually met the escape criteria, but the investigator did not recognize the fact. Based on the raw data, it appeared that the patient met the escape criterion at Week 4. The other patient (patient number 6333) was rolled over to the open-label study LAM20007 at Week 4 by mistake, according to the sponsor's email response. The patient had an increase in partial seizure frequency but did not meet the escape criteria.

There were 2 placebo group subjects (# 6229 and # 6372) who discontinued prematurely for reason of protocol violation. The sponsor noted that patient # 6229 supposedly did not meet the historical baseline seizure rate criterion (however the NDA showed that this patient had 350 partial seizures/week for the historical baseline). This patient subsequently was shown to have innumerable seizure activity all throughout the OLP and the randomized phase (? possibly on every treatment day of each phase) but was counted as having 0 seizure for the terminal OLP and for the randomized phase. Patient # 6372 had the lamotrigine dose (total 90 mg daily; presumably 30 mg TID) erroneously (error between the physician and pharmacist) reduced too rapidly during the randomized phase and was classified as a treatment failure patient who met all 6 escape criteria while spending 6.86 weeks in the randomized phase. Supposedly, this patient's 25 % weekly reduction in total lamotrigine dose was not based upon the total daily dose in the terminal OLP (90 mg/day) but on a total daily dose of 30 mg/day and this patient was thought to have received 21 mg/day for the first week instead of 75 mg day according to the sponsor. Thus, this patient could have experienced seizure activity that met escape because of too rapid taper possibly contributing to withdrawal-induced seizure.

Secondary Efficacy Results

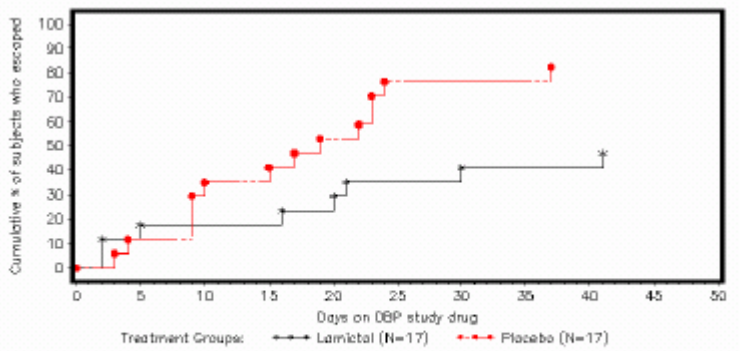
Time to escape patterns
As shown in Figure 2 and Figure 3, escapes occurred more rapidly in the placebo group.

Figure 2 Plot of Time to Escape Pattern for ITT DBP Population



Median time to escape for LTG is 42 days compared to 22 days for PBO (log rank p-value= 0.0590)
NOTE: Cumulative % of subjects who escaped are estimated by Kaplan-Meier method.
NOTE: Subjects who completed the DBP are right censored at 56 days (8 weeks).

Figure 3 Plot of Time to Escape Patters Per Protocol DBP Population



Median time to escape for LTG is 56 days compared to 19 days for PBO (log rank p-value= 0.0553)
NOTE: Cumulative % of subjects who escaped are estimated by Kaplan-Meier method.
NOTE: Subjects who completed the DBP are right censored at 56 days (8 weeks).

P values presented are nominal p values that have not been adjusted for multiplicity. In the ITT DBP population, twice as many subjects had met escape criteria in the placebo group (6 subjects) compared to the lamotrigine group (3 subjects) by Week 2. The median time to escape was 42 days in the lamotrigine group compared with 22 days in the placebo group (p=0.059). A similar response was seen in the PP DBP population, with the difference between treatment groups approaching statistical significance (p = 0.055).

Change in seizure frequency

Open Label Phase

A summary of percentage change in OLP partial seizure frequency, final total daily dose (TDD), by concomitant AED group, and analyzed study week interval for the OLP efficacy population is summarized in Table 12.

Table 12 Percent Change in Partial Seizure Frequency, Final TDD, and AED Group in the OLP Efficacy Population (LAM20006)

AED Category	N	Median % reduction in seizure frequency[1]	n (%) of subjects with specified reduction in seizure frequency		Mean (range) Final TDD: mg/kg/day
			≥50%	100%	
Induced	122	46.7%	60 (49%)	24 (20%)	9.3 (0.4 – 16.2)
Non-Induced	50	74.3%	32 (64%)	16 (32%)	3.2 (0.1 – 5.4)
Combined	172	60.5%	92 (53%)	40 (23%)	Not Applicable

Source Data: Table 13.6, Table 13.7, and Table 13.14
1. Last 28 days of the OLP

During the last 28 days of treatment of the OLP, 53% (92/172) of subjects had a ≥ 50% reduction in the frequency of partial seizures with 23% (40/172) becoming seizure free. The response to lamotrigine treatment differed based on background AEDs. A greater proportion of subjects (64%) taking non-enzyme inducing AEDs (including VPA alone) had a ≥50% reduction in seizure frequency compared with those receiving an enzyme-inducing AED (49%). A similar pattern was observed among the subjects who became seizure-free.

Double Blind Phase
A Summary of Percent Change in DBP Seizure Frequency by Seizure Type for the ITT DBP Efficacy Population and the PP DBP is summarized in Table 13.

Table 13 Change in All Partial Seizures in DBP – ITT DBP Efficacy Population (LAM20006)

Treatment Group	N	n (%) of subjects with specified reduction in all partial seizures[1]	
		26% to 49%	≥50%
ITT DBP Population			
Placebo	19	1 (5%)	0
LAMICTAL	19	2 (11%)	4 (21%)
PP DBP Population			
Placebo	17	1 (6%)	0
LAMICTAL	17	2 (12%)	3 (18%)

Source Data: Table 13.8 and Table 13.9
1. Entries represent the number and percent of subjects with the specified response relative to the last 28 days of the OLP.

The number of subjects who continued to have a reduction in all partial seizures during the DBP was much greater in the LTG group than in the placebo group. A similar pattern was seen in both the ITT DBP and PP DBP efficacy populations. This was also reflected in the proportion of subjects who had an increase in seizure frequency during the DBP where 74% of subjects in the placebo group had a ≥50% increase in frequency compared with 26% of subjects in the LTG group in the ITT DBP population. A similar pattern was observed in the PP DBP population.

Sponsor Subgroup Analyses
Combined center summary of efficacy data by the subgroups of age, race, sex, AED group, and AED group by age for the ITT DBP efficacy and PP DBP efficacy

populations are presented in Table 14 and Table 15, respectively. The sponsor noted that there was no significant difference between treatments groups in the number of completers and the number of failures based on the subgroup analyses.

Table 14 Summary of DBP Subgroup Analysis of Efficacy Data - ITT DBP

	Placebo (N=19)			LAMICTAL (N=19)			
Strata Category	No. Subjs.	No. Completers	No. Failures	No. Subjs.	No. Completers	No. Failures	P-value [2]
Age (mos)							
< 6	1	1 (5%)	0	0	0	0	
6 - 12	6	0	6 (32%)	8	2 (11%)	6 (32%)	0.473
> 12	12	2 (11%)	10 (53%)	11	6 (32%)	5 (26%)	0.089
Race							
White	17	2 (11%)	15 (79%)	17	6 (32%)	11 (58%)	0.225
Black	0	0	0	0	0	0	
Asian	0	0	0	0	0	0	
American Hispanic	2	1 (5%)	1 (5%)	1	1 (5%)	0	1.000
Other	0	0	0	1	1 (5%)	0	
Sex							
Male	9	1 (5%)	8 (42%)	12	5 (26%)	7 (37%)	0.178
Female	10	2 (11%)	8 (42%)	7	3 (16%)	4 (21%)	0.593
AED Group [1]							
Induced	14	3 (16%)	11 (58%)	13	6 (32%)	7 (37%)	0.236
Non-Induced	5	0	5 (26%)	6	2 (11%)	4 (21%)	0.455
AED Group x Age							
Induced <6 mos	1	1 (5%)	0	0	0	0	
6-12 mos	4	0	4 (21%)	4	1 (5%)	3 (16%)	1.000
>12 mos	9	2 (11%)	7 (37%)	9	5 (26%)	4 (21%)	0.335
Non-Induced <6 mos	0	0	0	0	0	0	
6-12 mos	2	0	2 (11%)	4	1 (5%)	3 (16%)	1.000
>12 mos	3	0	3 (16%)	2	1 (5%)	1 (5%)	0.400

NOTE: Only subjects who met the escape criteria were classified as treatment failures.
[1] Induced = Enzyme Inducing AEDs, Non-Induced = Non-EIAEDs (including VPA alone)
[2] P-value for the comparison between treatment groups with respect to the number of treatment failures is based on a two-tailed chi-square (Fisher's) test.

Table 15 Summary of DBP Subgroup Analysis of Efficacy Data - PP DBP

Strata Category	Placebo (N=17) No. Subjs.	Placebo (N=17) No. Completers	Placebo (N=17) No. Failures	LAMICTAL (N=17) No. Subjs.	LAMICTAL (N=17) No. Completers	LAMICTAL (N=17) No. Failures	P-value [2]
Age (mos)							
< 6	1	1 (6%)	0	0	0	0	
6 - 12	5	0	5 (29%)	6	2 (12%)	4 (24%)	0.455
> 12	11	2 (12%)	9 (53%)	11	6 (35%)	5 (29%)	0.183
Race							
White	15	2 (12%)	13 (76%)	15	6 (35%)	9 (53%)	0.215
Black	0	0	0	0	0	0	
Asian	0	0	0	0	0	0	
American Hispanic	2	1 (6%)	1 (6%)	1	1 (6%)	0	1.000
Other	0	0	0	1	1 (6%)	0	
Sex							
Male	9	1 (6%)	8 (47%)	11	5 (29%)	6 (35%)	0.157
Female	8	2 (12%)	6 (35%)	6	3 (18%)	3 (18%)	0.580
AED Group [1]							
Induced	12	3 (18%)	9 (53%)	12	6 (35%)	6 (35%)	0.400
Non-Induced	5	0	5 (29%)	5	2 (12%)	3 (18%)	0.444
AED Group x Age							
Induced <6 mos	1	1 (6%)	0	0	0	0	
6-12 mos	3	0	3 (18%)	3	1 (6%)	2 (12%)	1.000
>12 mos	8	2 (12%)	6 (35%)	9	5 (29%)	4 (24%)	0.335
Non-Induced <6 mos	0	0	0	0	0	0	
6-12 mos	2	0	2 (12%)	3	1 (6%)	2 (12%)	1.000
>12 mos	3	0	3 (18%)	2	1 (6%)	1 (6%)	0.400

NOTE: Only subjects who met the escape criteria were classified as treatment failures.
[1] Induced = Enzyme Inducing AEDs, Non-Induced = Non-EIAEDs (including VPA alone)
[2] P-value for the comparison between treatment groups with respect to the number of treatment failures is based on a two-tailed chi-square (Fisher's) test.

Reviewer Comments

I have many concerns about many aspects related to efficacy including the study design, the conduct of the study, and the analyses of results. I have outlined my numerous concerns and questions in the following bullets.

- I have concerns with the study design because this design supposedly enrolled "responder" patients into the randomized, double-blind, placebo-controlled study phase.

Approximately 45 % of patients enrolled did not meet the ≥ 40 % "responder (reduction of partial seizure rate by ≥ 40 % relative to the historical baseline seizure rate (which may not be a precise or reliable estimate). Conceivably, if this historical baseline seizure rate

was an overestimate of the true seizure rate and if there was a "significant" placebo "response," it is possible that people who were not really lamotrigine responders could have been considered "responders."

- The number of patients studied in the randomized, placebo-controlled phase is extremely small (only 19/treatment group). Unless there is a marked treatment effect, it seems difficult to expect that such a relatively small number of patients could exhibit statistically significant results. The lack of robustness of these data is clearly demonstrated by the fact that reclassifying one lamotrigine treated patient (#6333, who was erroneously rolled over into the extension trial prematurely by the investigator) who had discontinued prematurely in a post-hoc analysis explored by the sponsor. This patient who had not met any escape criteria but who had been classified as a treatment failure because the protocol specified that premature discontinuations not for an adverse event would be considered a treatment failure, applying a "worst case" analytical approach. This post-hoc analysis resulted in a p value of 0.0363 for 53 % treatment failures for lamotrigine treatment vs 84 % % treatment failures for placebo. Dr. Yan (Statistical Reviewer) reviews this information in more detail. Her reanalyses applied the chi-square test (p = 0.0363) and the more conservative Fisher's exact test (p = 0.0789). Dr. Yan also applied the chi-square test with continuity correction (p = 0.081). Thus, one can see that reclassification of merely one patient resulted in approximately a 50 % reduction of each p value and a "statistically significant" result.

  Retrospectively, it seems that an error in sample size estimation was made many years ago by the sponsor. Initially, the sponsor had projected a 40 % treatment effect (placebo % treatment failure – lamotrigine % treatment failure. Using this treatment effect the sponsor had planned enrolling a larger number of patients for each treatment group. However, the sponsor subsequently proposed a larger treatment effect of 50 % and re-estimated sample size resulting in the numbers enrolled (total 38, 19/group). Upon my inquiry of the sponsor as to how the treatment effect had been estimated/projected, the sponsor was not able to confirm that this number was based upon realistic available data. It seemed like the treatment effect % was primarily a speculative number which increased because the sponsor had observed a larger than expected number of "responders" in the OLP who "responded" by reducing their seizure rate > 80 % relative to the historical baseline period which was not prospectively collected.

- Typically, most efficacy information from adjunctive studies of treatment of partial epilepsy in adults or pediatric patients are derived from trials collecting baseline seizure rate data prospectively and then randomizing all suitable patients in an "add-on" study to either placebo or AED (under evaluation) and assessing a response. (b) (4)

  (b) (4)

- It is not clear that the sponsor conducted independent analyses of efficacy results relative to what was submitted by the investigator. It seems that in many (if not most or perhaps even all) instances the sponsor may have merely recorded what had been submitted by the investigator without independently analyzing the data/information and verify that the information/analyses were correct. In one instance, through a series of e-mail inquiries with the sponsor, we learned about this potential problem/deficiency. The sponsor informed us that one patient (# 6336) randomized to lamotrigine treatment and who had seemingly discontinued prematurely and who had been listed as not having met escape criteria, had actually met escape criteria ($\geq$ 50 % seizure rate increment) after 4 weeks treatment. It was not possible for us to verify information because the sponsor did not submit CRFs for all randomized patients.

- It is not clear that the historical "baseline" seizure rate (based upon $\geq$ 1 week) which were used to assess whether each patient was a responder ($\geq$ 40 % weekly seizure rate reduction from pre-treatment) during the OLP is based upon reasonably accurate or precise data. The sponsor thinks that in many instances this information was obtained from diaries but it does not have original data source information for this measure nor can it specify the number of patients with actual diary information nor the duration for which such data may have been collected. Furthermore, although the sponsor uses this historical "baseline" period for assessing responders, in the OLP, it does not consider this information for assessing how the seizure rate may have changed for each treatment group during the randomized phase.

  It is interesting that if one compares each treatment group for the % seizure rate reduction at the end of the randomized phase and considered a treatment failure (as I have), that there appears to be relatively little difference in the proportion of "treatment failures." I considered that patients with < 50 % reduction in seizure rate change from the historical baseline seizure rate were treatment failure (Table 17, Table 18). By this consideration the placebo group had 26 % treatment failures and the lamotrigine group had 16 % treatment failures, exhibiting a treatment effect of only 10 % (compared to the sponsor's primary analyses relative to the terminal OLP showing 26 % treatment effect)! Furthermore, these analyses also show that many patients considered to have been a placebo treatment failure had marked reductions (90-99 % for patients 6372, 6000, and 6335) in seizure rate relative to the historical baseline.

  It is possible that these changes could reflect regression to the mean because the data used as the historical baseline rate were not accurate or representative of the true seizure rate.

Typically, pre-treatment seizure rate data are based upon actual prospectively collected data. However, this was not the case for these patients. As a "bottom line" impression, I am highly skeptical of the accuracy or precision of these data. As a corollary of this consideration, if these data were not very representative of individual patients, then it also seems that true "responders" may not have been identified for randomization.

- I do not think that there was a good and similar balance between the two treatment groups regarding several important characteristics/parameters at or prior to randomization. Despite randomization, I believe that imbalance among these characteristics/parameters potentially could have influenced results and biased the placebo group toward more experiencing treatment failures. Table 16 shows the frequency of seizure types relative to The placebo group seemed to have more severe seizure disorders as a group with 5 % of these patients having simple partial seizures alone compared to the 16 % in lamotrigine group alone and the frequency of simple partial seizures (regardless of other seizure types) was half that of the lamotrigine group. The placebo group (84 %) also had a much higher prevalence of complex partial seizures compared to the lamotrigine group (53 %). The prevalence of partial seizures evolving to generalized seizures or generalized seizures was rather similar in both groups. In addition, the placebo group appeared to have a more severe or more complex seizure disorder than the lamotrigine patients. The most noteworthy differences were that : 1) B or C seizures were more common in placebo (89 %) than lamotrigine (79 %); 2) B or C or D or seizures were more common in placebo (95 %) than lamotrigine (84 %); and 3) B + C seizures were more common in placebo (26 %) than lamotrigine (11 %).

Table 16 Prevalence of History Seizure Type (Partial/Generalized) in Lamotrigine and Placebo Treatment Groups

	Treatment Groups	
	Placebo	**Lamotrigine**
A ± other seizure types	4/19 (**21 %**)	8/19 (42 %)
B ± other seizure types	16/19 (**84 %**)	10/19 (53 %)
C ± other seizure types	6/19 (32%)	7/19 (37%)
D ± other seizure types	6/19 (32 %)	5/19 (26 %)
A alone, no B, C, or D	1/19 (**5 %**)	3/19 (16 %)
B or C	17/19 (**89 %**)	15/19 (79 %)
B or C or D	18/19 (**95 %**)	16/19 (84 %)
B + C	5/19 (**26 %**)	2/19 (11 %)
B + C + D	0 /19 (0 %)	0 /19 (0 %)
A + B + C + D	0 /19 (0 %)	0 /19 (0 %)

A = Simple partial seizures
B = Complex partial seizures
C = Partial seizures evolving to secondarily generalized tonic-clonic, clonic, or tonic seizures
D = Generalized seizures (convulsive or non-convulsive)

Another potentially important difference that could have biased the placebo group toward more treatment failures was that many more placebo (7/19 – 37 %) patients had a 0 seizure rate for the last 28 days of the OLP than the lamotrigine (2/19 – 11%). Patients with a 0 seizure rate essentially at baseline for the controlled phase were typically considered a treatment failure if they experienced a single seizure in the controlled phase. It would have been important to stratify the randomization with regard to this variable (i.e. 0 seizure rate in terminal OLP).

Most (6/7) of the placebo patients were considered treatment failures by the primary analysis. The only patient who was not considered a treatment failure was patient # 6229 who had all the innumerable seizure activity during the OLP and the randomized phase but who was inexplicably considered as having 0 seizures all throughout both treatment phases Four of these placebo patients with 0 seizures in the terminal OLP were considered a treatment failure with only a single seizure in the randomized phase (Table 17 shows the duration of treatment in this phase for each patient). One patient (#6335) was considered a treatment failure with only 2 seizures over 8 weeks (0 seizure in first 4 weeks and 2 seizures in last 4 weeks for 0.25 weekly seizure rate over whole phase but 0.5 seizure rate over last 4 weeks) in the randomized phase and another patient (# 6283) who had 13 seizures in the randomized phase clearly appeared to be a treatment failure. I would suggest that it is not a very strict criterion to consider that someone is a treatment failure for having only 1 seizure (or perhaps even 2 in the whole 8 weeks). One could argue that this might reflect the normal variation that occurs over time or perhaps be a slight deterioration of control but not really treatment "failure."

- The sponsor's algorithm for determining treatment failure employed a $\geq$ 50 % increment in weekly seizure rate observed over 4 weeks during the randomization phase compared to the terminal 4 weeks of the OLP. However, this escape criterion did consider the absolute weekly seizure rate in the OLP used for comparison. If the seizure rate were relatively low such as 0.25 (reflecting 1 seizure in 4 weeks in the OLP), then experiencing 2 seizures over 4 weeks in the randomized phase would yield a weekly rate of 0.5 and would reflect a 100 % increment defining "escape" as per this 50 % threshold. It is difficult to believe that a patient who had 1 seizure in 4 weeks in one phase who now has 2 seizures in another phase is truly a "treatment failure."

  I have applied 2 additional criteria for treatment failure by requiring :1) an absolute increment in seizure rate of $\geq$ 1.0 (i.e. at least 1 seizure/week) along with a $\geq$ 50 % increment; and 2) an absolute increment in seizure rate of $\geq$ 1.0 (i.e. at least 1 seizure/week) along with a $\geq$ 100 % increment ((Table 17, Table 18). Using the first criterion, the treatment failure were 42 % and 21% for placebo and lamotrigine, respectively, demonstrating a 21 % treatment effect (vs the sponsor's original 26 % treatment effect). Using the second, more stringent criterion, the treatment failure were 37 % and 21% for placebo and lamotrigine, respectively, demonstrating a 16 % treatment effect. As a sensitivity analysis, it seems that the treatment effect progressively decreases as one employs a more stringent criterion for defining treatment failure for this parameter.

- I have a serious problem with patient 6229 who was enrolled and who was not considered as a treatment failure. This patient supposedly had 1400 seizures over 4 weeks in the historical "baseline" period yield a weekly seizure rate of 350. This patient then was counted as have 0 seizures in the terminal OLP and 0 seizures in a 6 week randomized phase treatment with placebo. However, this patient was noted to have "innumerable" seizure activity (ISA, usually 1-3 episodes) in most if not all days of the OLP and also the randomized phase. As per the sponsor's analytical plan, patients with ISA were supposed to be assigned the maximal number of seizures that occurred on a previous day. Thus, despite this patient supposedly having 350 seizures/week prior to enrolling in the study and also having extensive seizure activity all throughout the whole 20006 study (both phases), this patient was classified as not having any seizures in either the OLP or the randomized phase. It seems difficult to understand why this patient seemingly had countable seizure prior to enrolling but innumerable seizures throughout the study which were not countable. One questions if this patients should be censored. The sponsor considered this patient to be protocol violator for the historical baseline criterion (although I am not precisely sure why) and did not count this patient in the per protocol analysis.

- The sponsor has clarified how a patient with a 0 seizure rate in the OLP and < 4 weeks data in the randomized phase should be counted to determine a treatment failure as per the protocol and analysis plan. Specifically the protocol noted : "If a subject had not reached 4 weeks in the DBP but had already experienced a total number of seizures ≥150% of the seizures of the Optimization Period, the subject was considered to have met the escape criterion." It was also noted in Listing # 18 that patients who had 0 seizure rate in the terminal phase of the last 4 weeks of the OLP and any seizure(s) in the randomized phase would be assigned a 100 % seizure rate increment. It is not clear when this analytical plan originated nor am I able to confirm that this was an amendment to the protocol or SAP. In response to my inquiry, the sponsor informed me that counting a patient who had 0 seizure in the terminal OLP as a treatment failure with at least one seizure in the randomized phase was not specifically amended in the protocol nor Statistical Analysis Plan (SAP) but this information was instructed to investigators in an investigator meeting on 1/25/02. I am not sure when the arbitrary assignment of 100 % rate was established nor upon what basis.

Table 17 Reviewer Summary of Efficacy and Treatment Failure Classifications by Sponsor and Reviewer for Patients Randomized to Placebo

Pt ID	Baseline Pre-Rx Weekly Seizure Rate (4Weeks)	OLP Term-inal Seizure Rate (4Weeks)	% Δ from Baseline/ Pre-Rx	Random-ized Seizure Rate-Wks 1-4 (#Wks)	% Δ from OLP * / % Δ from Baseline	Random-Ized Seizure Rate (Wks 5-8) (#Wks)	% Δ from OLP* / % Δ from Baseline	Random-Ized Seizure Rate (All Wks) (#Wks)	% Δ from OLP* / % Δ from Baseline	Sponsor Rx Failure Escape Reason	Reviewer Rx Failure : % Seizure Increase From OLP ≥ 50 % **And** Wkly Seizure Rate Δ from OLP ≥ 1.0	Reviewer Rx Failure : %Seizure Increase From OLP ≥ 100 % **And** Wkly Seizure Rate Δ from OLP ≥ 1.0	**Reviewer Comments**
6369	3.0	0.25	- 92 %	2.85(3.86)	+1040% / - 5 %	NA		2.85(3.86)	+1040% / - 5 %	Yes, A,B	Yes	Yes	
6372	23.0	0	- 100 %	0 (4)	0 % / - 100%	0.35(2.86)	+ 100% / - 98 %	0.15(6.86)	+100% / - 99 %	Yes,A,B,C, D,E,F	No	No	Too rapid AED taper, ? withdrawal seizure
6167	1.25	0	- 100 %	0.78(1.29)	+100 % / - 38 %	NA		0.78(1.29)	+100 % / - 38 %	Yes,A,B	No	No	Not Rx failure by more stringent criteria
6229	350	0	- 100 %	0 (4)	0 % / - 100 %	0 (2)	0 % / - 100 %	0 (6)	0 % / - 100 %	Yes,A	No	No	? censor, innumerable seizures during all Rx
5981	1.25	0.25	- 80 %	0.50 (4)	+ 100% / - 60 %	0.75 (4)	+ 200% / - 40 %	0.63 (8)	+152% / - 50%	Yes,A	No	No	Not Rx failure by more stringent criteria
5982	70.0	39.25	- 44 %	42.50 (4)	+ 8 % / - 39 %	48.0(4)	+ 22 % / - 31 %	45.25(8)	+ 15 % / - 35 %	No	No	No	
5983	29.0	4.0	- 86 %	6.50 (2)	+ 63 % / - 78 %	NA		6.50(2)	+ 63 % / - 78 %	Yes,C,D	No	No	
6000	53.0	3.75	- 93 %	5.25 (4)	+ 40 % / - 90 %	5.70(3.86)	+ 52 % / - 89 %	5.47(7.86)	+ 46 % / - 90 %	Yes,B	Yes	No	Not Rx failure by more stringent criteria
6201	1.0	0.25	- 75 %	0.50 (4)	+ 100 % / - 50 %	0.78(3.86)	+ 212 % / - 22%	0.64(7.86)	+ 156 % / - 36%	Yes,A	No	No	Not Rx failure by more stringent criteria
5779	54.75	12..75	- 77 %	56.0 (2)	+ 339 % / + 2 %	NA		56.0 (2)	+ 339 % / + 2 %	Yes,A	Yes	Yes	
6464	16.0	1.0	- 94 %	1.0 (4)	0 % / - 94 %	0 (3.86)	- 100 % / - 100 %	0.51(7.86)	- 49 % / - 97 %	No	No	No	
5759	93.25	44.75	- 52 %	80.75 (4)	+ 80 % / - 13 %	NA		80.75 (4)	+ 80 % / - 13 %	Yes,A,B	Yes	Yes	
5765	8.0	3.25	- 59 %	13.73(3.71)	+ 322 % / + 72 %	NA		13.73(3.71)	+ 322 % / + 72 %	Yes,A	Yes	Yes	
6452	1.0	0	- 100 %	1.75 (0.57)	+100 % / + 75 %	NA		1.75 (0 57)	+100 % / + 75 %	Yes,A	Yes	Yes	
6283	12.0	0	- 100 %	3.25 (4)	+100 % / - 73 %	0 (0.43)	0 % / - 100 %	2.94 (4.43)	+100 % / - 76 %	Yes,A,B	Yes	Yes	
6285	1.0	0	- 100 %	0.70 (1.43)	+100 % / - 30 %	NA		0.70 (1.43)	+100 % / - 30 %	Yes,A,B	No	No	
6330	14.0	1.5	- 89 %	4.50 (4)	+200 % / - 68 %	3.25 (4)	+ 117% / - 77 %	3.88 (8)	+ 159 % / - 72 %	Yes,B	Yes	Yes	
6332	325.0	41.25	- 87 %	45.75 (4)	+ 11 % / - 86 %	16.75 (4)	- 59 % / - 95 %	31.24 (8)	- 24 % / - 90 %	No	No	No	
6335	42.0	0	- 100 %	0 (4)	0 % / - 100 %	0.50 (4)	+100 % / - 99 %	0.25 (8)	+100 % / - 99 %	Yes,A,B	No	No	Not Rx failure by more stringent criteria

Any seizures in randomized treatment phase are arbitrarily counted as + 100 % increment if 0 weekly seizure rate in OLP

Escape criteria : A=increment ≥ 50 %(≥ 150 % if , 4 wks); B=doubling highest 2D seizure frequency; C=onset new & more severe seizure; D=Clin significant worsening non-partial seizures; E=Need for epilepsy intervention Rx; F=Status epilepticus

Table 18 Reviewer Summary of Efficacy and Treatment Failure Classifications by Sponsor and Reviewer for Patients Randomized to Lamotrigine

Pt ID	Baseline/ Pre-Rx Weekly Seizure Rate (4Weeks)	OLP Term-inal Seizure Rate (4Weeks)	% Δ from Baseline/ Pre-Rx	Random-ized Seizure Rate Wks 1-4 (# Wks)	% Δ from OLP* / % Δ from Baseline	Random-ized Seizure Rate Wks 5-8 (# Wks)	% Δ from OLP* / % Δ from Baseline	Random-ized Seizure Rate (All Wks) (# Wks)	% Δ from OLP* / % Δ from Baseline	Sponsor Rx Failure Escape Reason	Reviewer Rx Failure : % Seizure Increase From OLP ≥ 50 % **And** Wkly Seizure Rate Δ from OLP ≥ 1.0	Reviewer Rx Failure : % Seizure Increase From OLP **> 100 % And** Wkly Seizure Rate Δ from OLP ≥ 1.0	**Reviewer Comments**
6371	18.0	1.75	- 90 %	12.38(1.86)	+607% / - 31 %	NA		12.38(1.86)	+607% / - 31 %	Yes,A,B,E	Yes	Yes	
6356	58.0	0	- 100 %	0 (4)	0 % / - 100 %	0 (4)	0 % / - 100 %	0 (8)	0 % / - 100 %	No	No	No	
6166	1.0	0.5	- 50 %	0.75 (4)	+50% / - 25 %	0 (0.86)	- 100 % / - 100 %	0.62 (4.86)	+ 24% / - 38 %	Yes,A	No	No	Not Rx failure by more stringent criteria
6124	35.0	9.25	- 74 %	1.75 (4)	- 81 % / - 95	13.48(3.86)	+ 46 % / - 61 %	7 51(7.86)	- 19 % / - 79 %	Yes,A	No	No	Not Rx failure by more stringent criteria
6233	199.5	0	- 100 %	0 (4)	0 % / - 100 %	5.0 (4)	+100% / - 97 %	2 50 (8)	+100% / - 99 %	Yes,A,B	Yes	Yes	
5684	21.0	11.5	- 45 %	13.5 (4)	+17 % / - 36 %	7.26 (4)	- 37 % / - 65 %	10.44 (8)	- 9 % / - 50 %	No	No	No	
5861	280.0	25.75	- 91 %	84.0 (0.86)	+226% / - 70 %	NA		84.0 (0.86)	+226% / - 70 %	Yes,B,E	Yes	Yes	
6059	1.25	0.75	- 40 %	1. 0 (4)	+33 % / - 20 %	1.17 (4)	+ 56% / - 6 %	1.03 (4.86)	+ 37% / - 18 %	Yes,A	No	No	Not Rx failure by more stringent criteria
5781	14.0	0.5	- 96 %	0 (4)	- 100 % / - 100 %	0 (3.86)	- 100% / - 100 %	0 (7.86)	- 100% / - 100 %	No	No	No	
6479	29.25	18.25	- 38 %	91 (0.29)	+399% / +211 %	NA		91 (0.29)	+399% / +211 %	Yes,B	Yes	Yes	
6480	19.25	10	- 95 %	16.58(2.71)	+66% / - 27 %	NA		16.58(2.71)	+66% / - 27 %	Yes,E	No	No	Not Rx failure by more stringent criteria
6442	10.0	6.5	- 35 %	8.68(3.57)	+ 34 % / - 13 %	NA		8.68(3.57)	+ 34 % / - 13 %	Yes	No	No	Not Rx failure by more stringent criteria
6282	28.0	2.25	- 92 %	0.78(3.86)	- 65 % / - 97 %	1.75(4)	- 22 % / - 94 %	1 27(7.86)	- 44 % / - 95 %	No	No	No	
6329	21.0	10.25	- 51 %	0.25 (4)	- 98 % / - 94 %	0 (4)	-100 % / -100 %	0 13 (8)	- 98 % / - 99 %	No	No	No	
6331	70.0	4.0	- 94 %	4.5(4)	+ 13 % / - 94 %	1.5(4)	- 63 % / - 98 %	3.0(8)	- 25 % / - 96 %	No	No	No	
6333	56.0	35.75	- 36 %	16.25(4)	- 55 % / - 94 %	3.5(0.29)	- 90 % / - 94 %	15.4(4.29)	- 57 % / - 73 %	No	No	No	
6334	51.75	2.75	- 95 %	1.0(4)	- 64 % / - 98 %	1.0(4)	- 64 % / - 98 %	1.0(8)	- 64 % / - 98 %	No	No	No	
6336	358.0	0.75	- 100 %	1.25(4)	+ 67 % / - 100 %	0.5(2)	- 33 % / - 100 %	1.0(6)	+ 33 % / - 100 %	No	No	No	
6309	70.0	12.0	- 83 %	5.0(4)	- 58 % / - 93 %	9.5(4)	- 21 % / - 86 %	7.78(8)	- 35 % / - 89 %	No	No	No	

Any seizures in randomized treatment phase are arbitrarily counted as + 100 % increment if 0 weekly seizure rate in OLP

Escape criteria : A=increment ≥ 50 %(≥ 150 % if , 4 wks); B=doubling highest 2D seizure frequency; C=onset new & more severe seizure; D=Clin significant worsening non-partial seizures; E=Need for epilepsy intervention Rx; F=Status epilepticus

One placebo patient (#6167) seems to illustrate a possible problem for interpreting treatment failure with these considerations. This patient was classified as having met the "50 %" threshold increment and a doubling of highest, consecutive 2 day OLP seizure count. Considering that this patient had 0 seizure rate in the OLP and 1 seizure in 1.29 weeks for a weekly seizure rate of 0.78, I cannot understand how this patient technically and officially met the criteria as outlined. It is not possible to ascertain that the patient had 150 % of the total number of seizures in the OLP because one cannot put obtain an increment of $\geq$ 150 % of the total number of seizures due to the inability to divide 1 by 0 (1/0) and come up with a real number!

- It is also worthy to note that the sponsor never submitted a Statistical Analysis Plan (SAP) to the DNP for review and when asked about the SAP, the sponsor noted that it had developed a SAP many years ago and had applied this SAP to its analyses which were submitted in this sNDA, but that it did not submit the SAP along with the sNDA. After our request that this SAP be submitted, the sponsor complied and submitted it.

- It is not clear that the sponsor and/or investigator analyzed the change in seizure rate (relative to the OLP) in the randomized phase as per the protocol which noted that "Monthly seizure frequency will be computed using the last 4 weeks of the optimization period and **the most recent 4 weeks** in the Double-Blind Phase." The NDA did not present results of such analyses. In response to my inquiry, the sponsor informed me : *"The data for evaluating the 50% threshold escape criteria was not evaluated on a weekly rolling week by week 4 week window (e.g., Weeks 1-4, 2-5, 3-6, 4-7, 5-8) . It was, however, evaluated on a by-visit rolling 4 week window. That is, at each visit during DBP, the most recent 4 weeks was evaluated. If the subject came in at Week 4, we used weeks 1-4. If the subject was delayed and came in at Week 5, we used weeks 2-5.* ***This is not reflected in Listing 18 where the data is lumped into 4 week buckets."***

  My interpretation would be that the most recent 4 weeks would be evaluated (relative to last 4 weeks of OLP on a rolling basis for weeks 1-4, 2-5,3-6, 4-7, and 5-8. If one only evaluated the data on a rolling basis by 4 weekly "buckets" at specific visits (which ordinarily occurred at 2 week intervals (start of study, week 2, week 4, week 6, week 8), it is theoretically possible that the 50 % criterion might be met an earlier time point before the visit (e.g. weeks 2-5) but then was not met at later, subsequent 4 week "buckets" because there were no subsequent seizures over the rest of the randomized treatment phase. If this was to happen, it is possible that the patient who really met the 50 % increment criterion might not be classified as a treatment failure.

  If the analytical approach of evaluating changes in seizure rates at 4 weekly buckets at each visit was actually followed and used to assess if treatment failure occurred, it is extremely puzzling why these results were not presented in the NDA in contrast to the changes in seizure rates shown in the first 4 weeks (weeks 1-4), the second 4 weeks (weeks 5-8), and the total number of weeks in the randomized phase.

  Not only would it be desirable to see the analyses conducted on a rolling weekly basis throughout the randomized phase, but it would also be desirable to be able to review the CRFs for the randomized patients, especially the CRFs specifying information about meeting one or more "escape" criteria.

- It is theoretically possible that the study design of withdrawal of lamotrigine could have contributed to "withdrawal'" seizures and biased results against placebo and in favor of lamotrigine. However, the tapering of lamotrigine was supposed to be done relatively slowly (e.g. decrease 25 % of total daily lamotrigine dose weekly over 4 weeks) and it does not seem likely that this slow taper could have contributed to the treatment failures in the placebo group. Nevertheless, it is not possible to exclude the possibility that this study design approach may have confounded results.

While considering this issue, I would note that patient placebo-treated patient # 6372, who the sponsor considered a protocol violator because the total daily dose of lamotrigine was reduced to rapidly and this erroneous too rapid lamotrigine reduction could have contributed to a withdrawal-induced seizure and incorrect classification as a treatment failure from lack of lamotrigine (see earlier section Protocol Violators) .

- Another study design potential problem was allowing patients with a history of generalized seizures to enroll in this study. Not excluding such patients allowed patients with generalized seizure disorders unrelated to partial epilepsy possibly to meet one or more of the "escape" criteria without necessarily having anything to do with how well treatment was for partial seizures in this young population.

  In response to my inquiry, the sponsor informed me that detailed information on the specific type of generalized seizures (e.g. absence, kinetic, atomic, etc.) each patient had prior to enrolling in study 20006 was not collected.

- Considering my potential concern about using criteria not necessarily related to partial seizures (see my comments in section 6.1.2 General Discussion of Endpoints), there may only be one patient who may have been incorrectly classified by using one of these questionable (as per my perspective) criteria (clinical worsening of non-partial seizure, need for additional medical intervention for any seizure). One lamotrigine-treated patient (#6480) was considered to have met the escape criterion of requiring additional medical intervention to treat a seizure. Although this patient had experienced a 66 % increment in weekly seizure rate, he presumably was not considered to have "escaped" the 50 % increment seizure rate criterion because he was only studied for 2.71 weeks and did not have $\geq$ 150 % of the total number of seizures in the terminal OLP (e.g. presumably 40). One could question if this patient would have been a treatment failure if the medical interventional escape criterion was not permitted because it was allowing possible treatment failure classification for seizure activity that may not have been related to partial seizures.

- We are not certain in a parent/caregiver who observed only a generalized tonic-clonic seizure recorded it as a partial seizure that evolved to a generalized seizure of a generalized seizure not necessarily related to a partial seizure.

- Considering that the total number of patients in the primary ITT efficacy analysis is quite small, it is difficult to draw any serious conclusions (especially considering statistical differences) about subgroup analyses that the sponsor conducted for age, gender, race, concomitant AED type (induced vs non-induced) and for concomitant AED type according to age. Although the % of treatment failures for the ITT was double for the placebo group (53 %) vs that for the lamotrigine (26 %) in the oldest age subgroup (> 12 months), it is of interest that the treatment failures were numerically identical (32 %) for patients 6-12 months of age.

  Race was not assessable because 89 % of patients were Caucasian.

  Whereas the % of treatment failures was double for placebo (42 %) vs lamotrigine (21 %) in females, the % was numerically similar for placebo (42 %) vs lamotrigine (37 %) in males.

The subgroups analyses by concomitant AED showed a greater % treatment failure for placebo patients in the induced group (58 %) vs lamotrigine (37 %) in this subgroup and similar numerical % of treatment failures for placebo (26 %) vs lamotrigine (21 %) for non-induced subgroup.

The extremely small numbers for the concomitant AED by age subgroup are too small for any reasonable comments.

In general, the sponsor's per protocol analyses of subgroups were similar to those of the ITT group.

- I agree with Dr. Sharon's Yan's analysis that this is a failed study for efficacy based upon the primary analysis of the primary efficacy endpoint.

6.1.5 Clinical Microbiology

- Not applicable

6.1.6 Efficacy Conclusions

Sponsor Efficacy Conclusions

· The proportion of subjects who escaped in the DBP of the study was 84% in the placebo group and 58% in the LAMICTAL group; however, the difference did not reach statistical significance (p=0.07).

· The time to meet escape criteria was nearly twice as long in the LAMICTAL group (42 days) compared with the placebo group (22 days). The difference approached statistical significance (p=0.06).

· The response to LAMICTAL treatment differed based on background AEDs. During the last 28 days of the OLP, a greater proportion of subjects (64%) taking non-enzyme inducing AEDs or VPA alone had a ≥50% reduction in seizure frequency compared with those receiving an enzyme-inducing AED (49%) when compared to baseline.

· During the last 28 days of the OLP, over half of the subjects (53%) showed a ≥50% reduction in partial seizure frequency when compared to baseline.

· In a post-hoc analysis of the primary endpoint in which one of two subjects who withdrew early from the study due to a protocol violation was reclassified as a nontreatment failure, the difference in treatment failure rates (53% LTG vs. 84% PBO) was statistically significant (p=0.036).

· A post-hoc analysis of the primary endpoint using a one-sided Fisher's exact test with a mid-p correction also indicated a statistically significant difference between LAMICTAL and placebo (p= 0.0451).

· In the DBP, subjects in the LAMICTAL treatment group continued to display improvement in seizure control relative to the OLP. A post-hoc analysis of the difference between treatment groups in the proportion of subjects with a >25% reduction, >25% deterioration or no change in seizure frequency relative to the last 28 days of the OLP was statistically significant (p=0.049).

Statistical Reviewer (Dr. Sharon Yan) Summary and Conclusions (see Review for Additional Details)

"Statistical Issues and Collective Evidence
The study had a small sample size as 38 patients were randomized into the double-blind controlled phase. The study was targeted at pediatric patients of 1-24 months of age. However, only one patient in the age group of 1 to 6 months was randomized. Neither the primary endpoint analysis nor the key secondary endpoint analysis showed statistically significant treatment difference.

There are several errors in the efficacy data submitted. Errors involving two patients (patient number 6124 and 6336) have been identified. All of the identified errors should have been corrected if any quality control procedures were taken by the sponsor.

Conclusions and Recommendations

The LAM20006 failed to demonstrate that Lamotrigine is effective as an adjunctive therapy in the treatment of partial seizure in pediatric patients with epilepsy. There is no statistically significant treatment difference based on the analyses of proportion of patients who met escape criteria and time to meeting the escape criteria, the primary and the key secondary efficacy variable of the study."

Reviewer Conclusions

(b) (4)

- Based upon the primary efficacy analysis of the ITT population (confirm by our Statistical Review by Dr. Sharon Yan, ostensibly, this is a failed study which is not statistically significant ($p = 0.0737$ for chi-square statistic which may not be appropriate because of small sample size; $p = 0.151$ for Fisher's exact test which may be more appropriate). In agreement with this view, the sponsor acknowledges that the difference in treatment failures for the ITT analysis of the randomized phase did not achieve statistical significance ($p = 0.07$).

- Overall, my numerous concerns outlined in my Reviewer Comments about the study design, conduct, and analysis of the controlled trial phase of study 20006 do not allow me to have confidence in any result of the study, even if the ostensible p value reported by the sponsor was < 0.05.

(b) (4)

(b) (4)

- I am concerned about the relatively small number of patients studied in the randomized, placebo-controlled study phase (19 patients/treatment group of lamotrigine or placebo) which does not seem to facilitate the collection of robust/reliable data.

(b) (4)

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Reviewer Overview of Sponsor's Presentation and Analyses of Treatment-Emergent Adverse Events (TEAEs)

The sponsor did not submit an Integrated Summary of Safety (ISS) but submitted a Clinical Overview in which the sponsor combined results from both Study 20006 and Study 20007. The safety sections of the Clinical Overview

reviewed this combined safety experience which almost completely reflected open-label safety experience. The sponsor also provided a file with many combined data tables and listings from both studies in module 5.

Prior to presenting a more detailed review of the treatment-emergent adverse events (TEAEs) in both trials (20006 and 20007), I will review my major concerns related to the adequacy, reliability, quality, utility of the sponsor's analyses and presentation of safety TEAEs. I would note that many of these concerns/issues were also discussed with Dr. Charles Cooper, who is a CDER Medical Officer with expertise in coding and classification of TEAEs. Dr. Cooper agreed that much of the TEAE safety data for which I have outlined my concerns below appear to be largely unreliable both in quality and frequency presented.

1. **I have concerns about the reliability of many TEAEs that are clearly or essentially symptoms (as opposed to more objective physical findings or clinical laboratory abnormalities).** Symptoms are subjective clinical abnormalities that the patient can communicate to a clinical observer or another individual. It is difficult to understand how infants varying in age between 1-24 months would be able to communicate a variety of symptoms (e.g. nausea, dyspnea, malaise, reflux symptoms, etc.) listed as "raw" VTs (Sponsor's Table 5.25). Although the sponsor presented the frequency (i.e. incidence) of many symptoms "observed" in both clinical trials, I think that it is difficult to consider that these TEAEs that have been "captured" and coded and present according to their frequency provide any accurate representation of what actually occurred and was experienced by these infants/toddlers.

   I have discussed this concern/issue with clinicians who are familiar with subjects in a similar age range and none believe that it is feasible (except in unusual/exceptional circumstances) to collect accurately symptomatic information and describe the frequency of symptoms in this population. In particular, one could speculate whether a patient experiencing vomiting is nauseated but that would only appear to be speculative. Analogously, dyspnea or shortness of breath is a symptom and not identical or synonymous with tachyon, hyperventilation or labored breathing which are observable clinical physical findings which may be associated with dyspnea but which do not necessarily reflect or indicate dyspnea. Neither does it seem feasible that one could ascertain that one of these infants was experiencing the "raw" VT of malaise.

   In summary, I believe that any TEAEs that reflect symptoms cannot be considered to reflect accurately what was experienced by any infant/toddler in this population.

2. **There is some imprecise coding of VTs to Puts that difficult to understand with respect to what clinical information is supposed to be reflected.** For example, failure to thrive (VT) is coded to the PT of dysphasia, left hemispherectomy (VT) is coded to the PT of epilepsy, weakness (VT) is coded to the PT of asthenia, and congestion (VT) is coded to the PT of ill-defined disorder.

3. It is not clear that sponsor has followed guidelines for consistently coding VTs to PTs. For example, the sponsor has many identical or virtually VTs coded to different PTs. For example, VTs including "increased seizure(s)" have been coded to different PTs including complex partial seizures, convulsion, or grand mal convulsion.

4. The sponsor does not seem to have accurately characterized similar clinical adverse reaction syndromes using a "lumping" approach but has taken a "splitting" approach of characterizing TEAEs. I believe that the sponsor has characterized many VTs which may be reflecting the same or similar adverse event as various distinct and different PTs. I have significant difficulty trying to understand how these VTs that

were presented in the coding dictionary listing reflect a clinical adverse reaction that corresponds to different, distinct PTs. There are many examples, which I have outlined below, related to this concern.

For example, VTs such as "lack of appetite," decreased appetite" or "not eating well" and "poor PO intake," were coded to PTs of anorexia, decreased appetite, and markedly reduced dietary intake, respectively.

There were separate PTs for sedation and somnolence and many seemingly similar sounding raw VTs were coded to somnolence. It is not clear how one could ascertain that an infant or toddler were somnolent or sedated.

Many various "raw" VTs possibly suggesting some type of seizure activity have been coded to a variety of PTs including complex partial seizures, convulsion, epilepsy, grand mal convulsion, infantile spasms, myoclonic epilepsy, myoclonus, partial seizures, partial seizures with secondary generalization, and simple partial seizures. I do not have any reason to believe, with any confidence, that these TEAE characterizations to these many distinct PTs are reliable.

Adverse reactions reflecting many similar "raw" VTs and many similar but distinctly different "raw" (possibly reflecting the same adverse reaction) have been coded to many PTs including influenza like illness, influenza, nasopharyngitis, pharnygitis, respiratory tract infection, respiratory tract infection viral, rhinitis, upper respiratory tract infection, viral upper respiratory tract infection, nasal congestion, respiratory disorder, respiratory tract congestion, rhinorhea, and upper respiratory tract congestion. When one reviews the various "raw" VTs, one does not feel confident that the actual adverse reaction has been accurately captured and presented.

There were several PTs (asthma, bronchial hyper reactivity, bronchospasm, wheezing) that had been coded from similar sounding VTs that may be reflecting bronchospasm.

Finally, many seemingly similar "raw" VTs are coded to many rash related PTs including rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, and rash morbilliform. It is not clear that these many of these VTs are truly reflecting a differently characterized adverse reaction coded to the specific PT.

In general, this "splitting" approach has significant potential for underestimating the actual frequency of a particular clinical syndrome. It is not clear that there is any real advantage toward characterizing TEAEs in these infants/toddlers with this splitting approach in contrast to taking a seemingly more reasonable "lumping" approach of attempting to characterize what adverse reactions seem to have been experienced. Considering the overall difficulty in characterizing many TEAEs accurately in this very young population, I that a "lumping" approach would possibly help characterize adverse reactions more accurately.

5. The sponsor's presentation of TEAEs for studies 20006 (the lead-in/open-label phase and the randomized, double-blind, placebo-controlled study phase for "responders") and 20007 only showed PTs and organ system class terms but did not exhibit higher level group terms. In the absence of such higher level group terms, it was not possible to ascertain whether the many various TEAEs that were coded to various PTs that presumably were reflecting seizures, might suggest a much higher frequency of seizures than was suggested by the analysis in which possible seizure-like activity was coded to many different PTs.

Considering the difficulty that may be associated with accurately characterizing seizures in very young pediatric patients (e.g. infants and toddlers), I do not think that one can be confident that the frequency of seizure activity was captured very accurately. The fact that blinded reading of video EEGs presently seems to be the gold standard for quantifying bonafide seizure activity (including partial seizures) as an efficacy endpoint emphasizes the uncertain nature of the quality and quantity of various seizure activity as TEAEs in these studies.

6. There are some TEAEs for which is it extremely difficult to understand what type of clinical experience/adverse reaction (if any) had actually occurred.

   The following represent the investigator reported raw terms and the PTs to which they had been coded.

PT	Investigator Reported Raw Term
Negativism	Oppositional behavior
Nervous system disorder	Neurological disturbances
Abnormal behavior	Behavioral deterioration
Aggression	Aggressive behavior
Antisocial behavior	Decreased interaction and activity
Emotional disorder	Screaming outbursts suspect headaches

   I suggest that it is impossible to understand what was actually observed and whether the event observed was really an adverse reaction, particularly one of potentially serious concern, rather than perhaps within the bounds of "normal behavior" of an infant or toddler.

7. Most of the experience observed for which there are safety data reflects open-label treatment. Open-label treatment is not considered to reflect frequencies of TEAEs observed in randomized, double-blind, placebo-controlled studies. To support this perspective, I have provided tabular data (Table 33), derived from the study of topiramate for adult migraine prophylaxis) that shows that Open-Label incidence markedly underestimates the frequency of TEAEs compared to the frequency obtained in placebo-controlled studies. Dr. Chuck Cooper (Medical Officer in Division of Bioinformatics VI, Office of Biostatistics) informed me that open-label data is typically recognized as underestimating the frequency of TEAEs of placebo-controlled trials.

8. The controlled treatment phase was based upon very limited, small number of patients studied in a randomized, double-blind, placebo-controlled drug withdrawal study setting (only 19 patients/treatment group for relatively short period up to 8 weeks). The average number of weeks in the double-blind phase for placebo patients was 5 weeks. Eight placebo-treated patients were followed in this study phase for $\leq$ 4 weeks.

9. The randomized, double-blind, placebo-controlled study phase does not reflect the safety experience that would be observed if all patient were treated with lamotrigine during a titration period to an "optimal" dose. Furthermore, of potentially significant impact, many TEAEs (for a variety of titrated drugs) often occur more frequently in the titration period rather than in the maintenance period (that was part of the placebo-controlled phase). Thus, the study design would have focused on the placebo-controlled safety experience after patients had been selected for this controlled study phase studies selected pts who tolerate lamotrigine and were at a maintenance dose

10. The safety experience in the randomized, double-blind, placebo-controlled withdrawal study phase consists of mostly pts on EI AEDs or "neutral" AEDs and few patients taking concomitant VPA which might put patients at the greatest risk for TEAEs.

11. There were no analyses of the titration (typically the phase in which many patients are more frequently experiencing TEAEs and/or TEAEs less commonly observed in the maintenance phase) vs maintenance phases for either study 20006 or 20007.

12. There is no presentation of TEAEs also by the number of events. The results are only presented as an incidence to indicate the number of patients with a TEAE regardless of the number of times that the TEAE occurred.

In the following sections, I have frequently presented the combined safety experience for both studies. When appropriate or seemingly potentially relevant, I have provide information from a single study or the brief placebo-controlled phase of Study 20006. These combined data do not reflect the relatively small and limited safety experience submitted in the Safety Update of a relatively few patients who continued to be treated for a relatively short time after the initial NDA data cut-off.

7.1.1 Deaths

A total of seven deaths were reported in the clinical development program. There were no deaths reported during LAM20006. Seven subjects died during participation in LAM20007. None of the events were judged to be related to study medication. Three of the deaths were due to pneumonia occurring from 7 to 10 months after onset of treatment with lamotrigine. All three of these subjects had previously identified risk factors for pneumonia including excessive bronchial secretions, gastroesophageal reflux and severe neurological impairment. One of these deaths, an infant with holoprosencephaly, followed a decision by the family to not resuscitate or intubate the infant. Brief narratives for these seven subject deaths are provided here.

· Approximately 10 months after starting LAMICTAL in the current trial, Subject 8040 was hospitalized for a fifth episode of pneumonia. He had a history of symptomatic epilepsy with complex partial seizures and infantile spasms and was receiving a prescribed LAMICTAL dose of 15.6mg/kg/day along with concurrent phenytoin, phenobarbital, and vigabatrin. Despite receiving treatment with azithromycin, the pneumonia did not resolve and the subject died. The investigator considered the pneumonia to be possibly associated with a viral infection. Of note, the subject had a history of excessive bronchial secretions treated with bromhexine prior to entering the study.

· Approximately seven months after starting LAMICTAL in the current trial, Subject 8116 was hospitalized with a second episode of pneumonia. He was receiving a prescribed LAMICTAL dose of 5.1mg/kg/day along with concurrent clobazam and VPA. He did not respond to antibiotics and oxygen. The infant died six days later. According to the investigator, the pneumonia was probably due to aspiration caused by the concurrent disorder of encephalopathy with breathing and swallowing difficulties. He had been previously treated with LAMICTAL in LAM20006 and had a history of symptomatic epilepsy, gastroesophageal reflux, psychomotor retardation, and spastic tetraplegia.

· Approximately eight months after enrolling in the open-label study, Subject 7489 developed a mild cough and one week later began vomiting brown liquid. Unilateral pneumonia was diagnosed and the subject was admitted to the hospital. A few days later, the subject aspirated, body temperature decreased, and respiratory rate increased. Discussions were held regarding discharging the child home with hospice care; however, she died before discharge. Cause of death was respiratory failure and oxygen desaturation secondary to aspiration pneumonia. This subject had a history of symptomatic epilepsy due to semilobar holoprosencephaly. She had been previously treated in LAM20006 and was noted to have a button gastrostomy tube at baseline. At the time of admission, she was already being tapered off of LAMICTAL (from actual dose of 15.69mg/kg/day to 7.85mg/kg/day) due to left ventricular hypertrophy which the investigator believed to be reasonably attributable to study drug. While in the hospital, her dose of LAMICTAL was further tapered to 0.62mg/kg/day. She was also receiving concurrent phenobarbital and clonazepam.

· Six weeks after entering the continuation study from protocol LAM20006, Subject 7370 was admitted to the hospital with symptoms of abdominal discomfort and irritability. No source of infection was found. The subject began to have respiratory problems the next day. He was treated with antibiotics but his condition continued to deteriorate. The subject died three days after the onset of these events. An infection of unknown origin was diagnosed. Of note, this subject had a history of symptomatic epilepsy, arterial vascular malformation, apnea, heart rhythm changes, gastroesophageal reflux, gastrostomy tube, hypotonic quadriplegia, and profound mental retardation. At the time of the SAE, he was receiving a prescribed LAMICTAL dose of 5.1mg/kg/day along with concurrent topiramate.

· Subject 7372 was previously treated with LAMICTAL in the OLP of LAM20006 and was subsequently randomized to LAMICTAL in the DBP. He received LAMICTAL for approximately 8 months in LAM20006. Approximately four months after initiating treatment in the open-label continuation study, Subject 7372 developed respiratory difficulties. He was brought to the emergency room where he was pronounced dead due to respiratory failure. The autopsy report listed findings of marked hydrocephalus and patchy bronchopneumonia. No actual cause of death was stated. Baseline medical conditions at the time of entry into LAM20006 included gastroesophageal reflux, gastrostomy tube, Nissen fundoplication, cerebral palsy, hydrocephalus, and symptomatic epilepsy. At the time of death he was receiving a prescribed dose of LAMICTAL of 19.2mg/kg/day along with concurrent carbamazepine.

· Subject 8209 was previously treated with LAMICTAL for 23.7 weeks in protocol LAM20006. Twelve days after the first dose of investigational product in this study, Subject 8209 was found by her parents in the early morning, blue and without a heartbeat. They tried several times to resuscitate her without success. She was taken by ambulance to the hospital and was pronounced dead on arrival. The subject died from a cardiac arrest. She had been receiving a prescribed LAMICTAL of 18.0mg/kg/day along with concurrent phenobarbital and topiramate. When this subject enrolled in LAM20006, she was noted to have idiopathic epilepsy and the following baseline medical conditions: reflux, PEG placement, hypotonia, cerebral palsy, and static encephalopathy. She had experienced two prior episodes of respiratory arrest while participating in protocol LAM20006.

· Nine months after commencing the investigational product, and seven months after commencing the investigational product in the current study, Subject 8171 developed a severe intracranial bleed. The intracranial bleed was considered to be life threatening, disabling, and required hospitalization. After fifteen days duration, the outcome of the intracranial bleed was reported to be fatal. According to the investigator, a possible cause of the intracranial bleed was hydrocephalus. On the date of onset of the intracranial bleed, the subject was receiving a

prescribed dose of LAMICTAL of 5.1mg/kg/day along with concurrent VPA. The subject had previously been treated in protocol LAM20006 and had been noted to have hydrocephalus and hypothyroidism at Screen along with symptomatic epilepsy.

Reviewer Comment

It is difficult to suggest that lamotrigine had anything to do with any of these 7 deaths. Of interest, 4 seemed related to infection from pneumonia, one seemed related to infection/sepsis from an unidentified source, one appeared to be a sudden death, and another appeared related to an intracranial bleed without any specification of bleeding diathesis. There were no new deaths in the limited safety experience updated in the Safety Update.

7.1.2 Other Serious Adverse Events

In LAM20006 and LAM20007 combined, a total of 98 (38%) subjects experienced non-fatal SAEs (Table 21). All seizure and pneumonia were among the most common (≥5%) SAEs reported during the studies. One subject during the OLP of LAM20006 and two subjects in LAM20007 experienced cases of rash that were considered SAEs.

LAM20006 Double-Blind Phase
Two subjects, one in the placebo group and one in the LAMICTAL group, experienced a SAE during the DBP of LAM20006. The placebo-treated subject experienced status epilepticus which was an escape criterion. The LAMICTAL-treated subject experienced bronchitis. Neither SAE was considered by the investigator to be reasonably associated with study drug administration.

Table 19 Most Common SAEs Occurring in > One Subject (Safety Population: Studies LAM20006 and LAM20007- Combined)

Adverse Event	Number (%) of Subjects LAM20006 and LAM20007Combined LAMICTAL N=256
Any Event	98 (38)
All seizure	48 (19)
Complex partial seizures	17 (7)
Status epilepticus	16 (6)
Convulsion	10 (4)
Partial seizures with secondary generalization	7 (3)
Grand mal convulsion	3 (1)
Simple partial seizures	3 (1)
Infantile spasms	2 (<1)
Myoclonic epilepsy	2 (<1)
Partial seizures	1 (<1)
Pneumonia	19 (7)
Pyrexia	10 (4)
Dehydration	9 (4)
Gastroenteritis	7 (3)
Apnea	6 (2)
Bronchiolitis	6 (2)
Upper respiratory tract infection	5 (2)
Bronchitis	5 (2)
Cyanosis	4 (2)
Vomiting	4 (2)
Respiratory distress	4 (2)
Viral infection	3 (1)
Gastrooesophageal reflux disease	3 (1)
All rash	3 (1)
Rash	2 (<1)
Angioneurotic oedema	1 (<1)
Urticaria	1 (<1)
Otitis media	2 (<1)
Respiratory syncytial virus infection	2 (<1)
Diarrhea	2 (<1)
Bronchopneumonia	2 (<1)
Infection	2 (<1)
Aspiration	2 (<1)

Data Source: Table 5.18

Reviewer Comment

- The sponsor's tables showed SAEs in > 1 patient. I reviewed the complete table of all SAEs and thought that there were several SAEs that occurred only in one patient but which were worthy of mention. These SAEs included : intracranial hemorrhage, aspiration pneumonia, respiratory arrest, respiratory failure, sleep apnea syndrome, and cardiac arrest. However, it is difficult to suggest that lamotrigine necessarily had anything to do with these SAEs for which there were corresponding narratives provided. Although I reviewed narratives for SAEs (and discontinuations for TEAEs), it is difficult attaching any lamotrigine causality to the various TEAEs.

- The most common SAEs ($\geq$ 4 % incidence) occurring almost totally in the open-label phase of each study were all seizures, pneumonia, pyrexia, dehydration, and gastroenteritis (in descending order of frequency).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The patient disposition for the open-label phase of study 20006 and 20007 and these combined studies are shown in Table 20, Table 21, and Table 22, respectively.

Across the two studies, a total of 170 unique subjects (66%) were prematurely withdrawn from treatment (Table 22). A total of 38 subjects who prematurely discontinued from the OLP of LAM20006 were allowed to enroll in LAM20007 on a case by case basis and also prematurely discontinued from LAM20007. Because the overall total in Table 22 reflects a subject's last reason for discontinuation from a study, it is not a summation of the individual study totals.

Table 20 Subject Disposition (Open-Label Phase, LAM20006)

	Total
Number Enrolled OLP[1]	177
Number Prematurely Discontinued	139 (79%)
Reason for Discontinuation	n (%)
Failed to meet randomization criteria	80 (45)
Adverse event	14 (8)
Consent withdrawn	11 (6)
Protocol violation	6 (3)
Other	28 (16)
Number Randomized to DBP[2]	38

Source Data: Table 12.2
1. OLP = Open Label Phase
2. DBP = Double-Blind Phase

Table 21 Subject Disposition (All Subjects Population: LAM20007)

Subject Status	Number (%) of Subjects
Enrolled	206
Completed	135 (66)
Prematurely Discontinued	71 (34)
Reasons for Discontinuation	
Consent Withdrawn	19 (9)
AE	18 (9)
Lack of Efficacy	16 (8)
Other	13 (6)
Lost to Follow-Up	2 (<1)
Protocol Violation	3 (1)

Data Source: Table 6.2 in LAM20007 aCSR
"Other" = Lack of compliance (1 subject); CZP (clonazepam) stopped, needed to increase LTG quicker (1 subject); surgical evaluation (1 subject); on VPA (1 subject); starting ketogenic diet (1 subject); ketogenic diet flu in Miami (1 subject); approaching second birthday (1 subject); epilepsy surgery (1 subject); scheduled for cardiac surgery (1 subject); will start vigabatrin (1 subject); late diagnosis of metabolic disorder (1 subject); moving out of state (1 subject); could not cross border to Lebanon due to political tension (1 subject)

Table 22 Subject Disposition (Studies LAM20006 and LAM20007-Combined)

	Number (%) of Subjects				
	LAM20006		LAM20007	Overall Total	
Subject Status	Placebo	LAMICTAL	LAMICTAL	Placebo	LAMICTAL
Total Exposures[a]	19	177	204	19	256
Prematurely Discontinued	0	141 (80)	67 (33)	0	170 (66)
Reasons for Discontinuation					
Failed to meet randomization criteria	0	80 (45)	NA	0	58 (23)[b]
AE	0	14 (8)	18 (9)	0	31 (12)[c]
Inadequate response to treatment	0	0	15 (7)	0	15 (6)
Administrative	0	19 (11)	21 (10)	0	34 (13)[d]
Other[e]	0	28 (16)	13 (6)	0	32 (13)[f]

Data Source: Table 5.1, Table 5.2, Table 5.3.
NA=Not Applicable.
a. Entries are the number of unique subjects who received at least one dose of study drug within a study.
b. A total of 22 subjects discontinued due to failure to meet randomization criteria in LAM20006 but discontinued due to another reason in LAM20007.
c. For the AE category, Subject 6230 discontinued due to an AE in LAM20006 and LAM20007.
d. Administrative includes lost to follow-up, consent withdrawn and protocol violations. Three subjects discontinued due to an administrative reason in both LAM20006 and LAM20007 (Subjects 5882, 6333 and 6704). In addition, three subjects (Subjects 6336, 6461, and 5921) discontinued due to an administrative reason in LAM20006 but discontinued due to another reason in LAM20007.
e. Other reasons for discontinuation are described in LAM20006 CSR Section 6.1 and LAM20007 CSR Section 6.1.
f. Three subjects (Subjects 5804, 5862, and 6168) discontinued due to other in both LAM20006 and LAM20007. In addition, six subjects (Subjects 6023, 6125, 6280, 6337, 6699, and 6739) discontinued due to another reason in LAM20007.

Reviewer Comment

- Of interest, Table 22 shows that nearly half (45 %) of the patients who enrolled in the open-label phase of study 20006 failed to meet the randomization criteria, the main one being that the patients demonstrated at least a $\geq$ 40 % "response" (i.e. decrease of 4 week seizure rate by $\geq$ 40 % relative to the historical seizure rate). Given my questions that I have raised previously about the accuracy/reliability of the historical seizure rate and the possibility that the number (and %) of "responders" may have been overestimated in the OLP of study 20006, it seems possible that the potential for an unselected population (as would occur in the "real world) to experience therapeutic benefit from lamotrigine may be even less than it would seem if the "responders" identified were truly "responders."

7.1.3.2 Adverse events associated with dropouts

Adverse Events Leading to Withdrawal
Adverse events leading to discontinuation in the individual studies are summarized in Table 23 and Table 24. The drop-outs/discontinuations for adverse events from both studies combined is shown in Table 25. Of the 256 unique subjects exposed to lamotrigine, 31 (12%) subjects were withdrawn due to an AE (Table 25). Of these, 12 (5%) subjects were discontinued due to a SAE. The most common SAEs leading to withdrawal of lamotrigine were seizure-related events (2%) consisting of complex partial seizures, myoclonic epilepsy and status epilepticus. One subject discontinued due to an SAE in both LAM20006 (Subject 6230, seizure-related AE) and LAM20007 (Subject 8151, seizure-related AE).

Table 23 Adverse Events Leading to Premature Discontinuation in ≥ 1% of Subjects of OLP in Study 20006

	Open Label Phase
Adverse Event	LAMICTAL N=177 n (%)
Subjects with ANY AE, n (%)	14 (8%)
Rash[1]	8 (5)
Rash	5 (3)
Urticaria	2 (1)
Rash Maculo-Papular	1 (<1)
Myoclonic epilepsy	2 (1)
Complex partial seizures	2 (1)

Source Data: Table 14.18

1. All rash included: rash, erythema, urticaria, rash macular, rash maculo-papular, rash erythematous, and rash papular.

Table 24 Adverse Events Leading to Premature Discontinuation in ≥ 1% of Subjects in Study 20007

Adverse Event	Number (%) of Subjects Discontinued N=204
Any Event	18 (9)
Pneumonia	4 (2)
Complex Partial Seizures	3 (1)
Status Epilepticus	3 (1)
All Rash	3 (1)
Rash	1 (<1)
Rash Generalized	1 (<1)
Rash Morbilliform	1 (<1)
Pyrexia	2 (<1)

Data Source: Table 7.18 in LAM20007 aCSR

Table 25 Adverse Events Leading to Premature Discontinuation in More than One Subject (Safety Population: Studies LAM20006 and LAM20007-Combined)

	Number (%) of Subjects
Adverse Event	LAM20006 and LAM20007 Combined LAMICTAL N=256
Any Event	31 (12)
All rash	11 (4)
Rash	6 (2)
Urticaria	2 (<1)
Rash generalized	1 (<1)
Rash maculo-papular	1 (<1)
Rash morbilliform	1 (<1)
All seizure	9 (4)
Complex partial seizures	4 (2)
Status epilepticus	3 (1)
Myoclonic epilepsy	2 (<1)
Infantile spasms	1 (<1)
Pneumonia	4 (2)
Pyrexia	2 (<1)

Data Source: Table 5.21

Reviewer Comment

- I suggest that the profile for drop-outs for TEAEs for the OLP of study 20006 is a better index of this parameter and of the type of TEAEs that may be of concern than looking at these type of drop-outs for study 20007 or both studies combined. I believe this because the results of study 20007 and the combined analyses of both studies include predominantly patients who rolled over from studied 20006 and who had already demonstrated tolerability to lamotrigine. The main reason for drop-out in new patients enrolling to study 20006 appeared to be rash (5 %).

7.1.3.3 Other significant adverse events

- There were no "other significant adverse events" (e.g. serious rash; serious rash is defined in the label as a rash associated with hospitalization and the discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis) of interest that prompted study discontinuation. However, any rash was a relatively common cause for study discontinuation.

7.1.4 Other Search Strategies (including review and analyses of TEAEs of special interest)

Two AEs of special interest, "All Rash" and "All Seizures" are discussed in this section.

Rash
Rash (defined as rash, urticaria, rash maculo-papular, erythema, rash macular, rash erythematous, rash papular, angioneurotic edema, rash generalized, rash morbilliform) is an AE of special interest, especially in the infant population. During the early development of lamotrigine a higher incidence of both rash and serious rash was noted in pediatric subjects compared to adults.

Table 26 summarizes the overall incidence of rash, rash attributable to study drug, rash leading to study discontinuation, rash reported as SAEs, and serious rash in studies LAM20006 and LAM20007 combined. A listing of lamotrigine subjects with rash reported as a treatment emergent AE in all studies was provided. The relationship of duration of exposure to rates of occurrence of all rash-related events was also presented and summarized.

In LAM20006 and LAM20007 combined, the overall incidence of rash on LAMICTAL was 20% (52 subjects) with all cases being mild or moderate in intensity with the exception of one severe case. This was higher than the incidence of rash reported in the individual studies; where rash was reported in 26 (15%) subjects in LAM20006 during the OLP, one (5%) subject randomized to LAMICTAL during the DBP, and 28 (14%) subjects in LAM20007. The rash rate of 14% reported in LAM20007 does not account for 24 subjects who experienced a rash in LAM20006 and, therefore, is lower than the rash rate reported within this integrated safety analysis. Of the 24 subjects who experienced a rash in LAM20006 that were not summarized in the LAM20007 CSR, 14 were exposed to lamotrigine in LAM20007 while 10 of these subjects did not participate in LAM20007. In LAM20006 and LAM20007 combined, rash was considered to be related to lamotrigine for 10 (4%) subjects and 11 (4%) subjects prematurely discontinued study drug due to rash. Both the overall rate of rash and the rate of discontinuation are similar to those experienced by older pediatric and adult patients. In current LAMICTAL/lamotrigine product labeling, serious rash is defined as a rash associated with hospitalization and the discontinuation of LAMICTAL or rash reported to be Stevens- Johnson Syndrome or toxic epidermal necrolysis. While 3 (1%) subjects (Subject 6216 in LAM20006; Subjects 8080 and 7850 in LAM20007) experienced a case of

rash on lamotrigine that was reported as a SAE, there were no cases of serious rash as defined in the lamotrigine product label as none of these three subjects discontinued LAMICTAL due to the rash. There were no cases of Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Excluding the three rash SAEs noted above, five subjects (Subjects 5720, 5801, 6042, 6461, and 6462) in LAM20006 and two subjects (Subject 7392 and Subject 7492) in LAM20007 had non-serious rash AEs reported during the same time period of other SAEs. Two of these subjects (Subjects 5801 and 6042) in LAM20006 discontinued lamotrigine due to rashes that were possibly caused by lamotrigine according to the investigator. One of these subjects in LAM20007 (Subject 7392) discontinued the study due to the rash and pyrexia. This was not considered to be a serious rash as the subject was hospitalized for treatment of aggravated seizures. Narratives for these cases are presented in the study reports.

During the DBP of study LAM20006, one case of rash was reported for a subject (Subject 6282) randomized to LAMICTAL that was mild in intensity. The subject remained in the study.

Table 26 Incidence of Rash (Safety Population: Studies LAM20006 and LAM20007- Combined)

	Number (%) of Subjects			
	LAM20006 OLP	LAM20006 DBP	LAM20007	LAM20006 and LAM20007 Combined
Adverse Event Category	LAMICTAL N=177	LAMICTAL N=19	LAMICTAL N=204	LAMICTAL N=256
All Rash	26 (15)	1 (5)	28 (14)	52 (20)
All Rash Attributable to Study Drug	6 (3)	0	4 (2)	10 (4)
All Rash Leading to Study Discontinuation	8 (5)	0	3 (1)	11 (4)
All Rash Considered to be SAEs	1 (<1)	0	2 (<1)	3 (1)
Serious Rash[a]	0	0	0	0

Data Source: Table 5.10, Table 5.12, Table 5.18, Table 5.21; LAM20006 CSR Table 14.8, Table 14.11, Table 14.12, Table 14.17, Table 14.18; LAM20007 CSR Table 7.6, Table 7.8, Table 7.16, and Table 7.18

a. In current LAMICTAL product labeling, serious rash is defined as a rash associated with the use of LAMICTAL that requires hospitalization and discontinuation of LAMICTAL or rash reported to be Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Seizure-Related Adverse Events

Seizure-related AEs in the individual studies were summarized in both study reports In studies LAM20006 and LAM20007 combined, a total of 68 (27%) subjects had seizure-related AEs (Table 27). The composite "All Seizure" term included the following terms: status epilepticus, complex partial seizures, convulsion, partial seizures with secondary generalization, grand mal convulsion, infantile spasms, simple partial seizures, myoclonic epilepsy, partial seizures, febrile convulsion and myoclonus. The seizure event was considered to be a SAE for 48 (19%) subjects. Investigators considered 10 (4%) of these seizure related AEs to be attributable to lamotrigine.

A total of 9 (4%) subjects were withdrawn from the study due to the seizure-related AE, none of them serious. Four of these subjects (Subjects 5800, 6061, 6230/8151, 6281) withdrew from LAM20006 or LAM20007 in part or in whole due to increased myoclonic seizure activity. One subject (Subject 5800) withdrew consent after only 4

weeks of treatment with lamotrigine while another (Subject 6061), experiencing a 'mild' increase in myoclonic seizure, withdrew for lack of efficacy after twenty weeks of treatment.
\
Only one subject (Subject 6230/8151) withdrew specifically for increased myoclonic seizure activity. This subject withdrew from LAM20006 for this reason after 15 weeks of treatment but continued into LAM20007 in association with the discontinuation of carbamazepine as a background AED. This subject later withdrew from LAM20007 after 11 additional weeks of treatment with lamotrigine due to increased complex partial and myoclonic seizures. A listing of lamotrigine subjects with seizure reported as a treatment emergent AE in LAM20006 and LAM20007 combined was provided. The relationship of duration of exposure to rates of occurrence of all seizure related events was also presented and summarized.

Table 27 Incidence of Seizure-Related Adverse Events (Safety Population: Studies LAM20006 and LAM20007- Combined)

	Number (%) of Subjects LAM20006 and LAM20007 Combined LAMICTAL N=256			
Seizure-Related Adverse Event	AE	Drug-related AE	AE leading to discontinuation	SAE
All Seizure	68 (27)	10 (4)	9 (4)	48 (19)
Status epilepticus	25 (10)	1 (<1)	3 (1)	16 (6)
Complex partial seizures	23 (9)	3 (1)	4 (2)	17 (7)
Convulsion	17 (7)	1 (<1)	0	10 (4)
Partial seizures with secondary generalization	11 (4)	2 (<1)	0	7 (3)
Grand mal convulsion	6 (2)	1 (<1)	0	3 (1)
Infantile spasms	4 (2)	0	1 (<1)	2 (<1)
Simple partial seizures	4 (2)	0	0	3 (1)
Myoclonic epilepsy	3 (1)	0	2 (<1)	2 (<1)
Partial seizures	2 (<1)	1 (<1)	0	1 (<1)
Febrile convulsion	1 (<1)	0	0	0
Myoclonus	1 (<1)	1 (<1)	0	0

Data Source: Table 5.10, Table 5.12, Table 5.18, Table 5.21

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Reviewer Comment

I did not note that the sponsor addressed this issue, which I think is extremely problematic in this very young population, and applicable to all clinical development programs for this very young age group.

- It is difficult to believe that many (and ? if hardly any) symptoms of TEAEs can be realistically be elicited from this population. Although some patients approaching 2 years old may be able to inform parents or the caregiver about some symptoms, I suggest that most patients in this 1-24 month age group are not likely to be able to give a history of symptomatic complaints that could be characterized as TEAEs. Considering that

we ordinarily characterize the safety of drugs not only on the basis of abnormal physical findings or behaviors but also to a significant degree on the basis of a large constellation of many various symptoms (e.g. nausea, fatigue, dizziness/light-headedness, pain, difficulty thinking, visual symptoms, etc), this is a serious problem that we encounter in attempting to characterize the safety profile fully (especially for TEAEs) an investigational drug.

- I have noted at the beginning of my Integrated Review of Safety (see section 7.1 Methods and Findings) my concerns about the sponsor characterization and coding of many TEAEs. Although it is possible to collect safety data based upon objective changes in physical findings on examination, possibly in behavior, vital signs, clinical laboratory tests, and ECGs, it is extremely difficult to collect safety data based upon symptomatic complaints in this very young population, which for practical considerations is not able to communicate very well, if at all!

- In contrast, I suggest that there are many changes in behavior that could potentially reflect, in general, symptomatic "complaints"/problems experienced by these infants and toddlers. For example, I think that it is possible that certain behavioral changes could reflect symptomatic complaints from an investigational drug. Some of these behavioral changes include increased irritability, crying, decreased feeding/eating, difficulty sleeping, and decreased crawling or walking. Of potential significant interest, some of these abnormalities seems to be reflected in Table 32 which describes the most common TEAEs in both studies. For example, 17 % experienced irritability, and 8 % experienced insomnia (possibly difficulty sleeping). I doubt that significant or special attention was focused on some of these other possible changes (e.g. crying, or decreased feeding/eating or decreased crawling or walking).

- I also think that it is interesting that 6 % experienced somnolence as a TEAE and 5 % experienced lethargy as a TEAE. However, I question whether there is a clear distinction between these PTs for this age group and suggest that it is possible that these different PTs may be reflecting the same adverse reaction, which could potentially be occurring with a much higher frequency than seemingly suggested (especially if most or all patients experiencing either somnolence or lethargy are mutually exclusive groups of patients). Thus, it is theoretically possible that 11 % of patients experienced somnolence/lethargy. It is also possible that "lethargy" could be reflecting decreased crawling or walking.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Reviewer Comment

- I have already outlined several of my concerns related to this topic (see my comments in section 7.1 Methods and Findings).

7.1.5.3 Incidence of common adverse events

Table 28 shows the most common TEAEs occurring in the OLP of study 20006.

Table 28 Most Common AEs (≥ 5%) reported During the OLP (LAM20006)

Adverse Event	LAMICTAL N=177 n (%)
Subjects with ANY AE	158 (89)
Pyrexia	73 (41)
Upper respiratory tract infection	33 (19)
Vomiting	33 (19)
Nasopharyngitis	29 (16)
All rash[1]	26 (15)
Constipation	24 (14)
Teething	22 (12)
Cough	21 (12)
Otitis Media	20 (11)
Diarrhea	19 (11)
Ear infection	17 (10)
Irritability	17 (10)
Complex partial seizure	12 (7)
Pharyngitis	12 (7)
Upper respiratory tract congestion	12 (7)
Dermatitis diaper	11 (6)
Nasal congestion	10 (6)
Insomnia	9 (5)
Bronchitis	8 (5)
Pneumonia	8 (5)
Somnolence	8 (5)

Source Data: Table 14.9

1. All rash included: rash, erythema, urticaria, rash macular, rash maculo-papular, rash erythematous, and rash papular.

All rash terms reported in this study and defined in the MedDRA dictionary (rash, erythema, urticaria, rash macular, rash maculo-papular, rash erythematous, and rash papular) were combined to report the incidence of rash. Twenty-six subjects (15%) reported rash during the OLP of the study (see Section 8.5.1).

Whereas Table 29 shows the most common (occurring in > 1 patient) TEAEs occurring in the DBP of study 20006, Table 30 shows the frequency of all TEAEs in each treatment group during the DBP.

Table 29 Most Common AEs (occurring in ≥ 2 subjects in either treatment group) Reported During the DBP (LAM20006)

Adverse Event	Placebo N=19 n (%)	LAMICTAL N=19 n (%)
Subjects with ANY AE	9 (47)	10 (53)
Pyrexia	2 (11)	2 (11)
Nasal congestion	1 (5)	2 (11)
Teething	3 (16)	0
Cough	0	2 (11)
Upper respiratory tract infection	0	2 (11)

Source Data: Table 14.14

Table 30 Summary of ALL AEs Reported During the DBP in Study 20006

	Placebo (N=19)				LAMICTAL (N=19)			
		No. of Subjs. w/ Max Intensity				No. of Subjs. w/ Max Intensity		
Body System Event	No. of Subjs.(%)	Mild	Mod	Sev	No. of Subjs.(%)	Mild	Mod	Sev
ANY EVENT	9 (47%)	3	6	0	10 (53%)	4	6	0
INFECTIONS AND INFESTATIONS								
ANY EVENT	1 (5%)	0	1	0	7 (37%)	3	4	0
UPPER RESPIRATORY TRACT INFECTION	0	0	0	0	2 (11%)	2	0	0
BRONCHIOLITIS	0	0	0	0	1 (5%)	0	1	0
BRONCHITIS	0	0	0	0	1 (5%)	0	1	0
EAR INFECTION	0	0	0	0	1 (5%)	1	0	0
EYE INFECTION	0	0	0	0	1 (5%)	1	0	0
INFLUENZA	1 (5%)	0	1	0	0	0	0	0
OTITIS EXTERNA	0	0	0	0	1 (5%)	0	1	0
PHARYNGITIS	0	0	0	0	1 (5%)	1	0	0
URINARY TRACT INFECTION	0	0	0	0	1 (5%)	0	1	0
VIRAL INFECTION	0	0	0	0	1 (5%)	0	1	0
GASTROINTESTINAL DISORDERS								
ANY EVENT	5 (26%)	1	4	0	1 (5%)	1	0	0
TEETHING	3 (16%)	0	3	0	0	0	0	0
CONSTIPATION	1 (5%)	0	1	0	0	0	0	0
DIARRHOEA	0	0	0	0	1 (5%)	1	0	0
DYSPHAGIA	0	0	0	0	1 (5%)	1	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (5%)	1	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
ANY EVENT	1 (5%)	0	1	0	5 (26%)	3	2	0
NASAL CONGESTION	1 (5%)	0	1	0	2 (11%)	2	0	0
COUGH	0	0	0	0	2 (11%)	1	1	0
APNOEA	0	0	0	0	1 (5%)	0	1	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
ANY EVENT	2 (11%)	1	1	0	2 (11%)	2	0	0
PYREXIA	2 (11%)	1	1	0	2 (11%)	2	0	0
NERVOUS SYSTEM DISORDERS								
ANY EVENT	1 (5%)	0	1	0	2 (11%)	0	2	0
CHORBOATHETOSIS	0	0	0	0	1 (5%)	0	1	0
SOMNOLENCE	0	0	0	0	1 (5%)	0	1	0
STATUS EPILEPTICUS	1 (5%)	0	1	0	0	0	0	0
PSYCHIATRIC DISORDERS								
ANY EVENT	2 (11%)	1	1	0	0	0	0	0
ABNORMAL BEHAVIOUR	1 (5%)	0	1	0	0	0	0	0
IRRITABILITY	1 (5%)	1	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
ANY EVENT	0	0	0	0	2 (11%)	2	0	0
ALL RASH [1]	0	0	0	0	1 (5%)	1	0	0
-URTICARIA	0	0	0	0	1 (5%)	1	0	0
HAIR GROWTH ABNORMAL	0	0	0	0	1 (5%)	1	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
ANY EVENT	0	0	0	0	1 (5%)	0	1	0
LYMPHADENOPATHY	0	0	0	0	1 (5%)	0	1	0
INVESTIGATIONS								
ANY EVENT	0	0	0	0	1 (5%)	1	0	0
CARDIAC MURMUR	0	0	0	0	1 (5%)	1	0	0

Table 31 presents the most common TEAEs in study 20007.

Table 31 Most Common AEs (≥ 5%) (LAM20007- 4 Month Safety Update)

Adverse Event	Number (%) of Subjects N=204
Any Event	177 (87)
Pyrexia	92 (45)
Upper Respiratory Tract Infection	58 (28)
Ear Infection	45 (22)
Cough	39 (19)
Vomiting	37 (18)
Irritability	35 (17)
Otitis Media	35 (17)
Constipation	33 (16)
Nasopharyngitis	29 (14)
All Rash[1]	27 (13)
Teething	27 (13)
Bronchitis	23 (11)
Pneumonia	23 (11)
Status Epilepticus	21 (10)
Pharyngitis	16 (8)
Diarrhea	16 (8)
Viral Infection	14 (7)
Upper Respiratory Tract Congestion	14 (7)
Complex Partial Seizures	14 (7)
Convulsion	13 (6)
Respiratory Tract Infection	13 (6)
Insomnia	13 (6)
Gastroenteritis	12 (6)
Nasal Congestion	11 (5)
Gastroesophageal Reflux Disease	10 (5)
Sinusitis	10 (5)
Tonsillitis	10 (5)

1. All rash included the following: angioneurotic edema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, and urticaria.

Data Source: Table 7.6 and Table 7.7 in LAM20007 aCSR

Table 32 indicates the most common TEAEs associated with lamotrigine in both studies combined.

Table 32 Most Common AEs (≥ 5%) (Studies LAM20006 and LAM20007- Combined)

Adverse Event	Number (%) of Subjects LAM20006 and LAM20007 Combined LAMICTAL N=256
Any Event	239 (93)
Pyrexia	135 (53)
Upper respiratory tract infection	74 (29)
All Seizure[a]	68 (27)
Vomiting	64 (25)
Ear infection	57 (22)
Cough	56 (22)
All rash[b]	52 (20)
Nasopharyngitis	50 (20)
Otitis Media	50 (20)
Teething	45 (18)
Constipation	44 (17)
Irritability	44 (17)
Diarrhea	31 (12)
Pneumonia	31 (12)
Bronchitis	29 (11)
Pharyngitis	23 (9)
Upper respiratory tract congestion	22 (9)
Nasal congestion	20 (8)
Insomnia	19 (7)
Respiratory tract infection	17 (7)
Viral infection	17 (7)
Gastroesophageal reflux disease	16 (6)
Somnolence	15 (6)
Dermatitis diaper	15 (6)
Gastroenteritis	14 (5)
Rhinorrhoea	14 (5)
Lethargy	12 (5)

Data Source: Table 5.10 and Table 5.11.

a. In the LAM20006 and LAM20007 combined, all Seizure AEs included: status epilepticus, complex partial seizure, convulsion, partial seizures with secondary generalization, grand mal convulsion, infantile spasms, simple partial seizures, myoclonic epilepsy, partial seizures, febrile convulsion.

b. In the LAM20006 and LAM20007 combined, all rash included rash, urticaria, rash maculo-papular, erythema, rash macular, rash erythematous, rash papular, angioneurotic oedema, rash generalized, rash morbilliform.

Reviewer Comment

- The most common TEAEs observed in the open-label lamotrigine treatment for studies 20006 and 20007 were generally similar. Thus, the combined analysis was also generally similar with the exception that "all seizures" were presented in this analysis and not in the separate analysis for each study.

- Although there were many TEAEs coded to PTs that occurred in one lamotrigine treated patient and no placebo patients in the randomized treatment phase, none seem very remarkable nor noteworthy. Two TEAEs for specific PTs (cough and upper respiratory tract infection) occurred in two lamotrigine patients and in no placebo patients. Of interest, the incidence of various infections was 7 fold higher in the lamotrigine group (37 %) vs placebo (5 %) and the incidence of various respiratory disorders was 5 fold higher in the lamotrigine group (26 %) vs placebo. Of additional interest, Dr. Norman Hershkowitz (DNP Medical Officer with expertise in epilepsy) informed me that based upon some informal reviews of infections associated with pediatric AED treatment, he is suspicious that there may be an increased risk of infections in pediatric patients taking AEDs. I believe that the frequency of the "grouped" data for PTs is certainly consistent with that hypothesis. Unfortunately, the study design for the controlled phase did not permit one to get a better assessment of this subject in these very young pediatric patients.

  Overall, I suggest that it was not too surprising to me that there were no major differences in the TEAE profile of lamotrigine vs placebo patients in the randomized phase based upon the frequency of specific PTs. I note this because these patients had typically already been treated with lamotrigine for many weeks and had been at a stable, "optimized," individually tolerated dose of lamotrigine.

- Dr. Charles Cooper (Medical Officer, Division of Biostatistics VI) is an expert on coding and characterizing TEAEs. He informed me that it is well known open-label trial experience/treatment typically underestimates the frequency of TEAEs. I considered this comment and evaluated it by comparing the incidence of certain, common TEAEs observed in randomized, double-blinded, placebo-controlled studies of migraine prophylaxis of adults with the highest dose studied (200 mg/day) of topiramate to the incidence of those same TEAE observed in the open-label, extension trials. Table 33 illustrates the results of my comparison.

  Table 33 shows that the open-label trial experience (vs experience in randomized, double-blinded, placebo-controlled studies) can markedly underestimate the drug associated incidence of TEAEs ranging from a 3 fold underestimation to a more than 14 fold underestimation (i.e. open-label experience reflects7 %– 33 % of incidence in double-blind, controlled experience). These results clearly corroborate the statement that Dr. Cooper noted to me about how open-label trials can markedly underestimate the frequency of TEAEs. My analysis did not address whether the severity of TEAEs may also be underestimated from open-label treatment experience.

Table 33 Comparison of Incidence (%) of Adverse Events with Drug Treatment in Controlled Studies vs Open-Label Studies and % Underestimation That Open-Label Studies Can Predict Adverse Events in Controlled Studies

Adverse Events	Results of Placebo-Controlled Studies for Migraine Prophylaxis			Results of Open-Label, Migraine Prophylaxis Extension Studies	% Underestimation Open-Label Studies Predict Adverse Events in Controlled Studies (Open-Label Drug % / Controlled Drug %)
	Treatment Effect (Topiramate - Placebo)	Placebo	Topiramate (200 mg/day	Topiramate (200 mg/day	
Paresthesia	43	6	49	6	12
Hypoesthesia	10	2	12	2	17
Dizziness	2	10	12	2	17
Language problems	5	2	7	2	29
Difficulty with memory	9	2	11	2	18
Anorexia	8	6	14	< 1	< 7
Depression	2	4	6	2	33
Difficulty with concentration/attention	8	2	10	1	10
Taste perversion	11	1	12	< 1	< 8
Weight decrease	10	1	11	3	27
Nausea	6	8	14	2	14
Diarrhea	7	4	11	2	18
Fatigue	8	11	19	2	11

- Table 34 provides my comparison of the incidence of TEAEs described in the lamotrigine label for randomized, double-blinded, placebo-controlled adjunctive study treatment of epilepsy in older pediatric patients (2-16 yrs) vs the incidence in mainly the open-label, combined lamotrigine experience in both studies 20006 and 20007. Although the sponsor did not provide an specific combined experience only from the open-label phase of each study, the overwhelmingly vast amount of the total data is derived from the open-label experience from both studies compared to the relatively small number of patients (19) treated in the randomized phase for a relatively short period ranging from 2 days up to 8 weeks.

  The overall safety profile seems quite different for the two populations for many TEAEs whether one looks at the lamotrigine experience in this young population (1-24months) vs the lamotrigine incidence or the lamotrigine treatment effect (lamotrigine % - placebo %). I suggest that there are marked differences in the frequency of many TEAEs which could be related to one or more of several potential explanations. These potential explanations/reasons include the possibilities that : 1) the open-label nature of the data underestimates the lamotrigine associated incidence (as shown by Table 33); 2) the corresponding

incidence for placebo (if it was available) for the young patients could be much different than for older pediatric patients in which case the treatment effect for this younger population could also be substantially different; 3) the TEAEs were not able to be elicited in the younger population because they are symptoms which could not be communicated by this population; 4) there was a different characterization/coding in the different populations; 5) the majority (~ 61 %, 125 /204)) of patients who enrolled in open-label safety study 20007 were "rollovers," who had previously been enrolled in study 20006 and because of their previously demonstrated lamotrigine tolerability would seem to have a decreased risk for experiencing TEAEs (compared to naïve patients enrolling in study 20007 and receiving lamotrigine for the first time); and/or 6) the younger population has a different sensitivity/susceptibility for experiencing the TEAEs related to pharmacokinetic and pharmacodynamic considerations.

The most striking difference occurs for the incidence of infections which is much higher 79 % for these young patients vs the incidence in the older children for infections for lamotrigine alone (20 %) or the for the lamotrigine treatment effect which is much smaller (3 %). It is not possible to know what the treatment effect is for this very young population because of the absence of placebo-controlled treatment not only for a longer period of time but also for the titration period in which some TEAEs mainly occur and/or more frequently. Knowing the treatment effect would be critical because one could argue that the risk for certain TEAEs might be similar for the younger population compared to the older population if the treatment effect was relatively similar Vomiting, constipation, and pyrexia are also substantially higher in this very young group of patients. Of little surprise but of significant interest, the incidence of many TEAEs that primarily reflect symptoms (e.g. nausea, asthenia, blurred vision, diplopia, pain, emotional lability), which could not be easily communicated by the very young patients was substantially lower than for older children Similarly, some TEAEs that could especially be related to walking (e.g. ataxia, gait abnormality, accidental injury) were also substantially less or not seemingly observed in the very young patients compared to the older patients.

The overall, apparent safety profile which is based primarily upon open-label experience (including roll-over of many patients who tolerated lamotrigine seems markedly different for these very young patients compared to that characterized for the older children from randomized, double-blinded, placebo-controlled studies of unselected patients

Table 34 Comparison of Incidence of Adverse Events in Placebo-Controlled of Adjunctive Lamotrigine Treatment in Older (2-16 yrs) Pediatric Epileptic Patients With Incidence of Adverse Events in Predominantly Open-Label Treatment (Combined Studies 20006 and 20007) in Younger Pediatric Patients (1-24 months)

Adverse Event	Adjunctive Pediatric (2-16 yrs) Placebo-Controlled Trials			Combined Studies 20006 and 20007 (1-24 months) (Mostly Open-Label Experience N = 256
	Placebo	Lamotrigine	Treatment Effect (Lamotrigine –Placebo)	Lamotrigine
Infection	17	20	3	79 Infections and infestations
Vomiting	16	20	4	27
Somnolence	15	17	2	6 + (lethargy 5, sedation 1, hypersomnia < 1)
Fever	14	15	1	45 Pyrexia
Dizziness	4	14	10	1
Accidental injury	12	14	2	Not specified
Pharyngitis	11	14	3	20 Nasopharyngitis
Rash	12	14	2	13
Ataxia	3	11	8	2
Diarrhea	9	11	2	12
Tremor	1	10	9	2
Abdominal Pain	5	10	5	2
Nausea	2	10	8	2
Asthenia	4	8	4	< 1
Flu syndrome	6	7	1	4 Influenza
Bronchitis	5	7	2	12
Increased cough	6	7	1	22 Cough
Pain	4	5	1	2
Diplopia	1	5	4	Not specified
Blurred vision	1	4	3	Not specified
Emotional lability	2	4	2	Not specified
Gait abnormality	2	4	2	< 1 Gait disturbance
Constipation	2	4	2	17
Urinary tract infection	0	3	3	3

7.1.5.4 Common adverse event tables

See previous section 7.1.5.4.

7.1.5.5 Identifying common and drug-related adverse events

Reviewer Comment

- It was not feasible to identify drug-related TEAEs in the absence of a significant treatment period (especially during lamotrigine dose escalation) that was conducted under randomized, double-blinded, placebo-controlled conditions.

7.1.5.6 Additional analyses and explorations

- There were no additional, exploratory analyses conducted for inclusion here.

7.1.6 Less Common Adverse Events

See section 7.1.5.3 (Incidence of Common Adverse Events)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The sponsor conducted limited analyses of clinical laboratory testing (measured at a central laboratory (b) (4)) for hematology analytes and clinical chemistry analytes and most of the data collected were in the open-label, uncontrolled conditions of Study 20006 and 20007.

Clinical hematology and chemistry samples were drawn at screening, week 8, end of OLP, final visit of DBP, and at the follow-up visit. Hematology and chemistry samples were analyzed (b) (4) for the following :

- Hematology : hemoglobin, hematocrit, red blood cell count, mean blood cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count ,and white blood cell count with differential
- Chemistry: sodium, potassium, total protein, albumin, creatinine, urea, bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, and glucose.
- Urinalysis

Clinically significant abnormal laboratory findings or other abnormal assessments that were detected after study drug administration or that were present at baseline and worsened following the start of the study were included as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study that did not worsen, were **not** included as AEs or SAEs.

The investigator exercised his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

Hematology, clinical chemistry, and urinalysis data were evaluated by descriptive statistics. Absolute change from screening values were summarized at each nominal visit. The median change from screen and two-sided 95% confidence intervals (CIs) based upon a Wilcoxon signed-rank test were computed at each post-baseline visit.

The sponsor presented these data analyses (e.g. mean absolute laboratory analyte over time, median change from screen/baseline, and frequency of clinically significant laboratory analytes) for the individual studies (20007, and OLP and DBP separately) and a combined analyses for the frequency of patients with "abnormalities of clinical significance." Of note, the sponsor did not indicate specifically whether the frequency of a clinically significant abnormality was related to a high or low abnormality, but presumably combined both types of abnormalities in the frequency. Neither did the sponsor provide a reference range for these analytes in its submission. When the reviewer asked for such a reference range list for all the laboratory analytes, the sponsor submitted 2 huge documents (~ 140 pages each) from the central laboratory (b) (4) that included all types of information about the laboratory in addition to the reference ranges.

Baseline versus minimum and maximum clinical laboratory values for various **sponsor selected** analytes were presented graphically for subjects treated with lamotrigine in all studies.

The sponsor noted that there were no clinically meaningful changes in hematology or clinical chemistry parameters attributed to LAMICTAL in LAM20006 and LAM20007. Treatment-emergent laboratory abnormalities were rare in LAM20006 and occurred in only one subject during the OLP of the study (increased alanine aminotransferase [ALT] and aspartate aminotransferase [AST] values) and the subject was withdrawn from the study. In LAM20007, there were no significant changes in mean values throughout the study for any of the parameters. There were isolated and transient occurrences of values exceeding reference ranges without an indication of a pattern or trend in these occurrence. Six subjects had isolated elevations of alkaline phosphatase levels that were considered clinically significant. None had associated elevations of AST or ALT. Two of these were attributable to laboratory error and the others to concomitant enzyme –inducing AEDs known to cause elevations of alkaline phosphatase. Seven subjects had transient elevations of AST and/or ALT none of which was attributed by investigators to lamotrigine. All of these elevations were in the 2-3 fold increase range for AST and ALT and none was associated with corresponding elevations of alkaline phosphatase or bilirubin. Subject 7491 had an episode of status epilepticus in the days prior to detection of the enzyme elevations indicating the enzyme increases may have been due to muscle activity. Subject 7509 had an apparent hypersensitivity reaction in association with AST and ALT elevations but the source of the reaction was not identified nor was it attributed to lamotrigine.

More specifically for study 20006, the sponsor noted that treatment-emergent changes were rare and only occurred in one subject during the OLP of the study (increased ALT and AST values) and the subject was withdrawn from the study.

More specifically for study 20007, the sponsor noted that six subjects (Subject 7829, Subject 7830, Subject 8114, Subject 8149, Subject 7491, and Subject 7852) had isolated elevations of alkaline phosphatase levels that were considered clinically significant. Values from two of these subjects (Subject 7852 and Subject 8114)

were believed to represent laboratory error. One subject (Subject 8149) had a normal value on retest. Each of the remaining three subjects was taking concomitant enzyme inducing AEDs known to cause elevations of alkaline phosphatase. Eight subjects (Subject 7370, Subject 7451, Subject 7469, Subject 7489, Subject 7491, Subject 7509, Subject 7852, and Subject 8240) had transient elevations of AST and ALT with an additional subject (Subject 7490) having an isolated elevation of ALT alone. None of these elevations was attributed by investigators to LAMICTAL. Values from two of these subjects (Subject 7852 and Subject 8240) were reported as possible laboratory errors with subsequent values that were reported as normal. All of these elevations were in the 2-3 fold increase range for AST and ALT and none was associated with corresponding elevations of bilirubin. Subject 7491 had an episode of status epilepticus in the two weeks prior to detection of the enzyme elevations indicating the enzyme increases may have been due to muscle activity.

Reviewer Comment

- I reviewed the sponsor's analyses and did not conclude that there were any clear changes from baseline for any analytes based upon median changes from screen (i.e. "baseline").

- Although the sponsor did not present specific analyses showing the frequency of LFT increments (e.g. aminotransferases suchs as serum ALT and/or AST) according to specific thresholds (e.g. > 3 X ULN, > 5 X ULN, etc), the sponsor noted that : "All of these elevations were in the 2-3 fold increase range for AST and ALT and none was associated with corresponding elevations of bilirubin." I suspect that some of these LFT increments were > 3 X ULN but were probably < 5 X ULN. For example in study 20006, patient # 6338 exhibited a serum AST 289 U/L and ALT 183 U/L at OLP week 8. In study 20007, patient # 7509 exhibited a serum AST 135 U/L and ALT 176 U/L at study week 24, patient # 7489 exhibited a serum AST 126 U/L and ALT 100 U/L at study week 24 (after 48 weeks total treatment), patient # 8240 exhibited a serum AST 73 U/L and ALT 170 U/L at study week 24, and patient # 7491 exhibited a serum AST 72 U/L and ALT 126 U/L at study follow-up.

  Overall, the frequency of investigator –judged clinically significant laboratory abnormalities for both studies combined was 3 % for ALT and 2 % for AST.

- It is conceivable that if the sponsor conducted a systematic assessment of laboratory abnormalities based upon specific criteria that the impression of outliers in these trials might be different.

- My impression is that it is difficult to exclude that lamotrigine was the cause of the abnormal LFT elevations, at least in some of these very young patients. This possibility, however, is not necessarily that unexpected in that the lamotrigine label notes that some patients can exhibit hepatotoxicity related to lamotrigine treatment.

- I also note that despite the fact that the sponsor submitted many tables showing the baseline versus minimum and maximum clinical laboratory values for sponsor selected (for which there was no explanation of why the analyte was selected) analytes were presented graphically for subjects treated with lamotrigine in all studies, the sponsor did not provide its interpretation of these figures depicted in the ISS tables.

- In summary, despite the fact that the sponsor conducted various clinical laboratory analyses, it is difficult to conclude that the sponsor conducted systematic analyses and seriously or critically reviewed these results to assess a possible effect of lamotrigine, even under primarily open-label treatment conditions.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The sponsor did not analyze analytes for the mean change from "baseline" but rather analyzed the 20006 data for the absolute analytes data over time (at end of OLP, at DBP week 8, at "follow-up") and also for the median change from screening (and also showed 95 % confidence interval-CI) for this last parameter at the different study times outlined. The sponsor conducted these analyses separately for all patients treated in the open-label phase and for the 2 treatment groups that had been randomized.

There were no significant changes in mean laboratory values throughout the study for any of the parameters. There were isolated and transient occurrences of values exceeding reference ranges without an indication of a pattern or trend in these occurrences.

Reviewer Comment

- I agree that the predominantly open-label treatment of lamotrigine did not suggest an effect of lamotrigine on the median change from screen/baseline for the various analytes.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor analyzed the data to show the frequency of "treatment of emergent clinically significant changes in lab values" However, the frequency of this "abnormality" term was not analyzed as per any defined abnormality because the designation of "clinically significant changes" was left to the subjective discretion of the investigator.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

- Not applicable

7.1.7.5 Special assessments

- Not applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The sponsor only measured and analyzed "vital sign" data for heart rate, weight, height, temperature, and head circumference.

In the Clinical Overview presenting the results of the combined analyses, the sponsor noted that there were no clinically significant changes from baseline in any of the vital sign data evaluated during studies LAM20006 and LAM20007.

Reviewer Comment

- There was no collection of blood pressure data in this very young population. Lamotrigine has the potential (as does any CNS acting drug) to alter blood pressure (especially lower blood pressure). Given this possibility and that the significant frequency of "dizziness" (which I do not think can exclude a decrease in blood pressure in at least some lamotrigine treated patients) observed in older pediatric patients (and adults), it is conceivable that lamotrigine could be exerting significant effects on blood pressure, an important vital sign parameter that was not collected (for unknown reasons). Although the lamotrigine label does not describe effects on blood pressure, I am not confident that data have been adequately collected and analyzed to demonstrate or exclude effects on blood pressure (especially related to changes of position and time of dosing). I cannot think of a good reason why blood pressure was not measured and collected throughout these studies. Furthermore, normative data exist for this very young population.

- Neither did the sponsor measure and present data on ventilatory rate.

- It did not appear that the sponsor collected any of the VS outlined according to any standardized, systematic methods/procedures.

- The sponsor did not conduct and present any analyses for weight, height, temperature, or head circumference.

- Overall, the sponsor did not collect some standard VS data (e.g. blood pressure and ventilatory rate) and did not conduct many standard/routine analyses of typical VS data collected.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The sponsor analyzed the open-label treatment of lamotrigine in studies 20006 (OLP) and 20007 and also the DBP of study 20006.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The sponsor noted that there was a trend for mean heart rate to decrease during the study in LAM20007 with the mean rate at screen being 118 beats per minute and 111 beats per minute at study termination. The mean values remained within the normal range. The sponsor believed that this change was due to the duration of the study. The normal heart rate decreases over time in infants, particularly comparing infants less than one year with those greater than one year of age. A similar trend was not observed in LAM20006.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

All recorded heart rate values for a given subject were compared to the age-specific critical range limits described in Table 35 in order to identify values of potential clinical concern within the integrated safety analysis. The subject's age at the time the heart rate value was recorded was used in this analysis.

Table 35 Sponsor's "Critical Range Limits for Heart Rate (bpm)"

Age (mos)	Lower Limit	Upper Limit
1-2	110	190
3-5	95	195
6-11	100	180
12-24	80	160
>24	65	150

Data Source: Biomedical Systems (LAM20006 CSR Attachment 2; LAM20007 CSR Attachment 3).

The sponsor noted that approximately 16% of the unique subjects exposed to lamotrigine had heart rate values below an age specific critical limit while only 4% of subjects had values above the critical limit for a subject's age.

The sponsor did not conduct any shift analyses nor any other outlier analyses relative to other specified outlier thresholds. "Clinical significant" abnormalities were left to the subject discretion of each investigator for VS abnormalities.

For study 20006, the sponsor noted that there were no clinically significant changes from baseline in any of the parameters evaluated during the OLP or DBP of the study.

For study 20007, the sponsor noted that there were no clinically significant changes from baseline in any of the vital sign data evaluated.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There was no special attention given to this topic. See above section 7.1.8.3.2.

7.1.8.4 Additional analyses and explorations

- Not applicable

7.1.9 Electrocardiograms (ECGs)

The ECG data for subjects who participated in both LAM20006 and continuation study LAM20007 were developed as contiguous records of ECG data. Treatment-emergent ECG abnormalities were analyzed within this submission. For all subjects, treatment-emergent ECGs were defined as those abnormalities that were reported for the first time post Screen. The screen assessment of LAM20006 was used to identify treatment-emergent ECGs for subjects who participated in LAM20006 and for subjects who participated in both LAM20006 and continuation study LAM20007. The screen assessment in LAM20007 was used to identify treatment-emergent abnormalities for the lamotrigine-naïve subjects who enrolled into continuation study LAM20007. ECG data in the integrated safety analysis were analyzed for LAM20006 and LAM20007 combined. Scatter plots of screen versus minimum and maximum ECG interval data were also presented. A total of 239 (93%) of the 256 unique subjects exposed to lamotrigine provided at least one post baseline ECG assessment.

The most frequent treatment emergent ECG changes for lamotrigine subjects were sinus tachycardia (6%), sinus bradycardia (5%), and right ventricular hypertrophy (3%). A listing of subjects with clinically significant (based upon investigator judgment and not according to criteria identified and applied by the sponsor) ECG abnormalities. Patient profiles were provided for patients with ECG abnormalities. . ECG data for the individual studies were also summarized in the final study reports for LAM20006 and LAM20007 CSR. The ECG results described were generated from the retrospective review and measurement of all ECG intervals (b) (4) These ECG data were reviewed by an external pediatric cardiologist whose report for each study was also submitted.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The ECG data for subjects who participated in both LAM20006 and continuation study LAM20007 were developed as contiguous records of ECG data. Treatment-emergent ECG abnormalities were analyzed within this submission. For all subjects, treatment-emergent ECGs were defined as those abnormalities that were reported for the first time post Screen. The screen assessment of LAM20006 was used to identify treatment-emergent ECGs for subjects who participated in LAM20006 and for subjects who participated in both LAM20006 and continuation study LAM20007. The screen assessment in LAM20007 was used to identify treatment-emergent abnormalities for the lamotrigine-naïve subjects who enrolled into continuation study LAM20007. ECG data in the integrated safety analysis were analyzed for LAM20006 and LAM20007 combined. Scatter plots of screen versus minimum and maximum ECG interval data were also presented. A total of 239 (93%) of the 256 unique subjects exposed to lamotrigine provided at least one post baseline ECG assessment.

The most frequent treatment emergent ECG changes for lamotrigine subjects were sinus tachycardia (6%), sinus bradycardia (5%), and right ventricular hypertrophy (3%). A listing of subjects with clinically significant (based upon investigator judgment and not according to criteria identified and applied by the sponsor) ECG abnormalities. Patient profiles were provided for patients with ECG abnormalities. . ECG data for the individual studies were also summarized in the final study reports for LAM20006 and LAM20007 CSR. The ECG results described were generated from the retrospective review and measurement of all ECG intervals (b) (4) These ECG data were reviewed by an external pediatric cardiologist whose report for each study was also submitted.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

A summary of ECG interval data was provided in for the OLP and DBP for study LAM20006 and for study LAM 20007.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Summary changes for ECG interval data for the OLP of study 20006 are shown in Table 36. In the OLP, there was a slight increase in PR mean change from Screen at the End of OLP visit and the Final/Premature Discontinuation (PD) visit. At the Final/PD visit, QRS mean change from Screen was slightly increased. The mean change from Screen for the uncorrected QT interval was slightly increased at the End of OLP visit. The mean changes from Screen for QTcF were not significant at any visit. There was a significant decrease in heart rate at the End of OLP visit. Sixteen subjects had treatment-emergent clinically significant abnormalities during the OLP. The treatment-emergent abnormalities included sinus bradycardia (8 subjects),
sinus tachycardia (5 subjects), first degree AV block (1 subject), and right ventricular hypertrophy (2 subjects).

During the DBP, there were no significant mean changes from Screen for PR, QRS, QTcF, or heart rate.

Table 36 Summary of ECG Interval Data during OLP for Study 20006

ECG Interval	Planned Relative Time	n	Median	Range	Mean Change from Screen	95% Confidence Interval
PR (seconds)	Screen	154	0.111	0.069-0.191		
	OLP Week 8	131	0.112	0.078-0.194	0.0022	(-0.0001, 0.0046)
	End of OLP	68	0.112	0.079-0.170	0.0071	(0.0030, 0.0113)
	Final/PD	65	0.114	0.068-0.198	0.0041	(0.0005, 0.0076)
QT (seconds)	Screen	153	0.278	0.205-0.360		
	OLP Week 8	132	0.281	0.200-0.343	0.0034	(-0.0009, 0.0077)
	End of OLP	68	0.279	0.213-0.385	0.0075	(0.0007, 0.0143)
	Final/PD	65	0.289	0.225-0.338	0.0052	(-0.0007, 0.0110)
QRS Duration (seconds)	Screen	154	0.071	0.042-0.091		
	OLP Week 8	132	0.070	0.051-0.098	0.0012	(-0.0002, 0.0026)
	End of OLP	69	0.070	0.049-0.095	0.0019	(0.0000, 0.0037)
	Final/PD	65	0.072	0.048-0.095	0.0029	(0.0010, 0.0049)
QTcF[1] (seconds)	Screen	153	0.355	0.298-0.453		
	OLP Week 8	132	0.358	0.275-0.409	0.0013	(-0.0028, 0.0054)
	End of OLP	68	0.354	0.291-0.406	0.0018	(-0.0038, 0.0075)
	Final/PD	65	0.361	0.316-0.420	0.0016	(-0.0038, 0.0071)
Heart Rate (beats/min)	Screen	154	128.0	82.0-195.0		
	OLP Week 8	132	124.5	67.0-190.0	-3.3279	(-7.6862, 1.0304)
	End of OLP	69	122.0	54.0-204.0	-6.9048	(-12.075, -1.7346)
	Final/PD	66	122.0	60.0-173.0	-5.7833	(-12.028, 0.4611)

Source: Table 14.26
1. QT correction was calculated according to Fridericia's formula.

The sponsor noted that the following mean changes (Table 37) from Screen for ECG interval data in study 20007 were within the 95% confidence intervals, and that the changes were not clinically significant according to the external pediatric cardiologist who reviewed the data.

Table 37 Summary of ECG Interval Data by Nominal Study Week (Safety Population: LAM20007 from the 4 Month Safety Update)

ECG Interval	Weeks on Therapy	n	Median	Range	Mean Change from Screen[1]	95% CI[2]
QT Interval (seconds)	Screen	188	0.279	0.21, 0.34	-	-
	Week 8	71	0.279	0.23, 0.35	-0.004	-0.010, 0.002
	Week 24	67	0.279	0.23, 0.35	-0.000	-0.006, 0.006
	Term[3]	75	0.279	0.23, 0.35	0.000	-0.005, 0.006
	Final/Follow-up	151	0.283	0.13, 0.38	0.005	-0.000, 0.010
QRS Duration (seconds)	Screen	189	0.069	0.04, 0.10	-	-
	Week 8	71	0.068	0.05, 0.09	0.001	-0.001, 0.002
	Week 24	67	0.071	0.05, 0.08	0.003	0.001, 0.005
	Term[3]	75	0.071	0.05, 0.08	0.003	0.001, 0.005
	Final/Follow-up	152	0.071	0.04, 0.10	0.003	0.002, 0.005
QTcF[4] Interval (seconds)	Screen	188	0.356	0.30, 0.42	-	-
	Week 8	71	0.354	0.31, 0.39	-0.002	-0.008, 0.004
	Week 24	67	0.360	0.31, 0.41	0.000	-0.004, 0.005
	Term[3]	75	0.357	0.31, 0.41	0.002	-0.003, 0.006
	Final/Follow-up	151	0.360	0.18, 0.42	0.001	-0.004, 0.006
PR Interval (seconds)	Screen	189	0.108	0.07, 0.17	-	-
	Week 8	71	0.108	0.08, 0.15	-0.000	-0.002, 0.002
	Week 24	67	0.112	0.07, 0.15	0.000	-0.003, 0.004
	Term[3]	75	0.111	0.07, 0.15	0.001	-0.002, 0.003
	Final/Follow-up	151	0.109	0.07, 0.17	0.002	-0.001, 0.004
Heart Rate (beats/min)	Screen	189	126.0	86.0, 202.0	-	-
	Week 8	71	125.0	64.0, 186.0	1.986	-3.392, 7.364
	Week 24	67	127.0	65.0, 173.0	0.119	-6.447, 6.686
	Term[3]	75	125.0	65.0, 173.0	0.676	-5.372, 6.724
	Final/Follow-up	152	121	70.0, 170.0	-6.352	-10.71, -1.998

Source: Table 7.27 in the LAM20007 aCSR
1. A negative difference indicates that the value at screen is higher than the value on treatment.
2. 95% CI based on a paired t-test
3. Represents the last on-study visit.
4. QT correction was calculated according to Fridericia's formula.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor did not conduct a formal analysis of outliers using specific thresholds for outliers nor any shift analyses. The sponsor presented information on "clinically significant" ECG abnormalities that had been subjectively determined by each investigator.

In LAM20006, 16 subjects had treatment-emergent clinically significant ECG abnormalities during the OLP consisting of sinus bradycardia (8 subjects), sinus tachycardia (5 subjects), first degree AV block (1 subject), and right ventricular hypertrophy (2 subjects). One placebo subject had a treatment-emergent clinically significant abnormality of sinus tachycardia during the DBP. One subject (Subject 5799) developed an AE of left ventricular hypertrophy documented by echocardiogram. The external pediatric cardiologist reviewed this subject's data and determined that, while the exact etiology of the left ventricular hypertrophy is not known, the possibility that it was related to study drug, though unlikely, could not be ruled out .

Overall, twenty-two subjects experienced 23 treatment-emergent clinically significant ECG abnormalities in study 20007. Four (2%) subjects had occurrences of sinus bradycardia, 11 (5.4%) subjects had occurrences of sinus

tachycardia, 1 (0.5%) subject had right axis deviation, and 7 (3.4%) subjects reported other ECG abnormalities (other included atrial premature beats [1 subject], right ventricular hypertrophy [5 subjects], and bi-ventricular hypertrophy [1 subject]).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There was no special attention given to this topic. See above section 7.1.9.3.2.

7.1.9.4 Additional analyses and explorations

Reviewer Comment

- Although the sponsor presented scatter plots of screen versus minimum and maximum ECG interval data were also presented, there was no explanation nor interpretation of these data.

Reviewer Comment

- The sponsor's analyses of the ECG data did not suggest any concern although the bulk of these data represented uncontrolled data analyses

7.1.10 Immunogenicity

Reviewer Comment

- There are no issues related to immunogenicity with the approved product, lamotrigine.

7.1.11 Human Carcinogenicity

Reviewer Comment

- The sponsor did not submit any new information related to carcinogenicity other than what is described in the label.

7.1.12 Special Safety Studies

Reviewer Comment

- There were no special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Reviewer Comment

- The sponsor did not submit any new information related to withdrawal phenomena and/or abuse potential other than what is described in the label.

7.1.14 Human Reproduction and Pregnancy Data

Reviewer Comment

- The sponsor did not submit any new information related to human reproduction and pregnancy data other than what is described in the label.

7.1.15 Assessment of Effect on Growth

Reviewer Comment

- The sponsor did not submit any information or analyses related to the effect of lamotrigine on growth (nor height or head circumference). Although the sponsor collected height information, the sponsor did not conduct analyses of the potential effect on growth. This theoretically could be done by analyzing Z scores in the open-label experience. However, because the sponsor did not provide specific guidance/guidelines about measuring height accurately/reproducibly in these infants/toddlers, I would suspect that the data collected would be of such poor quality that the chance of seeing an effect on growth would be very low unless the drug was producing a marked effect on slowing growth. I am not aware of an effect described in the label for effects of lamotrigine on slowing growth in older pediatric patients (2-16 yrs).

7.1.16 Overdose Experience

Reviewer Comment

- The sponsor did not submit any new information related to overdose experience other than what is described in the label.

7.1.17 Postmarketing Experience

The safety of lamotrigine is reviewed on an ongoing basis by the Global Clinical Safety and Pharmacovigilance department within GSK. It is GSK policy to review all incoming AE reports from all sources, including clinical trials (serious reports only), spontaneous reports (healthcare professional and consumer), regulatory authorities, published literature and from post-marketing surveillance studies. These data are analyzed in a cumulative setting to identify and assess potential new safety signals. Any adverse reactions identified during these reviews are incorporated into the GSK Core Safety Information (CSI) and subsequently into the local prescribing information, e.g. USPI. AEs which have been reported but not reflected in the CSI or USPI have either been isolated findings, poorly documented and thus unassessable, or there were other risk factors present such as concurrent illness or concomitant medications more likely to have caused or contributed to AE development. The information included in the CSI and USPI reflects the post-marketing experience with lamotrigine to date.

The GSK AEs database was searched up to 27 July 2006 to identify all post-marketing reports in children less than 24 months of age in which lamotrigine was reported as a suspect drug. A listing of post marketing reports in

children less than 24 months of age was provided. The search identified 87 reports. The majority of these reports were received from the United States (39%), United Kingdom (16%), Germany (14%) and France (5%). The reports were received directly from health care professionals (67%) or consumers (21%), indirectly from regulatory agencies (9%) or from the published literature (3%).

Deaths
Three reports of an AE with a fatal outcome were identified.

A0048628A: This report describes a 15 month old female child who was found dead. The child had a history of difficult to control multiple seizure types and had previously been treated with phenobarbital and carbamazepine. Valproate was subsequently used and **lamotrigine 12.5mg every other day added approximately three weeks later. Nineteen days later the lamotrigine dose was increased to 12.5mg daily. Two days after the child was found dead**; autopsy results were apparently inconclusive. The reporting physician considered the event to have been unlikely to be related to lamotrigine.

B0054011A: This report describes a 22 month old boy, with a history of febrile convulsions from the age of 4 months and minor motor seizures from the age of 8 months, who was hospitalized following a 45 minute episode of convulsive seizures. **The event occurred 14 days after starting lamotrigine** and 9 months after starting valproate. He was treated with phenytoin, phenobarbital and carbamazepine. He developed petechiae, followed the next day by **disseminated intravascular coagulation (DIC)** with facial swelling and **increased liver enzymes**. Lamotrigine was withdrawn. The child died 76 days after the onset of initial symptoms. The cause of death was considered to be severe encephalopathy and spasticity. **The reporter considered the events as possibly related to lamotrigine.**

B0123299A: This case, with few details, describes a 21 month old girl with encephalic cyst and hydrocephalus, secondary to congenital ventriculitis, **who developed Stevens- Johnson Syndrome and died 3 weeks after starting lamotrigine** (dose only specified as one quarter tablet twice daily). No causality assessment was specified by the reporter.

Serious Adverse Events
Including the 3 reports with a fatal outcome, 36 of the 87 reports were identified as serious reports. Some reports include AE terms in more than one MedDRA System Organ Class (SOC), but the most common SOC for the primary AE was Skin and Subcutaneous Tissue disorders (10), Nervous System disorders (5) and Metabolism and Nutrition disorders (4). The sponsor noted that the AEs reported are consistent with those reported in older children and adults and are either listed or do not suggest new safety signals.

Rash
Rash is an AE of special interest in the infant population as, during the early development of lamotrigine, a higher incidence of both rash and serious rash was noted in pediatric subjects compared with adults. The 10 serious AE reports identified in the Skin and Subcutaneous Tissues SOC were all reports of rash. The age of the child in the reports ranged from 7 to 22 months. The time to onset of event was available for 7 reports and ranged from 10 days to 8 weeks.

There were 6 reports of Stevens-Johnson Syndrome (including the report with a fatal outcome), one of toxic epidermal necrolysis, one of erythema multiforme and 2 of rash. Two of the reports of Stevens-Johnson Syndrome

Table 38 Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
Musculoskeletal and connective tissue disorders											
#D0045625A	Germany	MD	23M / M	TAB	3tab	2004 - Oct2004	(b) (6)	U	Rhabdomyolysis, Acute prerenal failure, Dehydration; Pneumonia, Shock;	Fatal	Indication: convulsions. Concurrent medical condition: lissencephaly. No concurrent medications. Lamotrigine was discontinued and the patient was rehydrated and treated with unspecified antibiotic . Approximately 4 months later the patient died due to pneumonia and circulatory failure.
Blood and lymphatic system disorders											
B0051205A	UK	RA	14M / F	PO	45mg	12FEB1997 - 24SEP1997	(b) (6)	7M	Pancytopenia, Liver function test abnormal, Gastroenteritis, Dehydration, Depressed level of consciousness ;	Improved	Concurrent valproate. Developed gasteroenteritis after 7M. Also noted to have increased LFTs, panctopenia (no values given). Improved on withdrawal of all AEDs.
Immune system disorders											
D0017464A	Germany	MD	19M / F	TAB	U	15Jan2001 - 28Jan2001	(b) (6)	15D	Drug hypersensitivity, Stevens-Johnson syndrome;	Resolved	-

Table 38 (Continued) Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
Blood and lymphatic system disorders											
#B0068051A	Austria	MD	18M / F	TABD	5mg	28MAY1999 - 13JUN1999	(b) (6)	2W	Disseminated intravascular coagulation, Hepatic function abnormal, Pyrexia, Rash;	Resolved	Co-suspect LTG & valproate. Reaction after 2w of LTG which was withdrawn. Events resolved.
Eye disorders											
#A0094929A	United States	MD CO	8M / F	PO	85mg	Feb1999 - 23Apr1999	U	U	Blindness, Convulsion;	Improved	-
Gastrointestinal disorders											
#A0056916A	United States	HP	19M / M	TAB	125mg	29JAN1997 - U	(b) (6)	U	Pancreatitis, Abdominal pain, Anorexia, Weight decreased, Lethargy;	Improved	History of oesophageal reflux. Concurrent topiramate. Amylase 94, lipase 524. Hospitalised, treated with IV fluids. Negative re-challenge.
Hepatobiliary disorders											
#D0001002A	Germany	MD OM	20M / F	TAB	7.5mg	28FEB1997 - 19MAR1997	(b) (6)	20D	Hepatic failure, Myoclonus, Tonic convulsion, Coagulopathy, Pneumonia, Life support;	Resolved	On phenobarbitone, valproate. Valproate withdrawn 14 days prior to onset of acute liver failure (20 D after start of lamotrigine). Lasted 5 days.

Table 38 (Continued) **Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug**

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
#B0346795A	Spain	MD	1Y / F	TAB	15mg	Feb2004 - 20Sep2004	(b) (6)	U	Hepatic failure, Pyrexia, Sepsis, Condition aggravated;	Unresolved	Indication: epilepsy. History of fits from birth caused by possible metabolic defect. Concurrent medication: phenobarbitone, topiramate, clobazam. Concurrent medical condition : sepsis. Reporting physician suspected event related to previous possible metabolic disorder and sepsis and unrelated to treatment with lamotrigine.
#A0040613A	United States	MD	8M / F	TAB	25mg	JAN1996 - JAN1996	(b) (6)	U	Hepatic failure, Irritability, Anorexia, Pyrexia, Dehydration;	Resolved	-

Table 38 (Continued) Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
Infections and infestations											
#B0060037A	UK	PH MD	19M / F	TABU	5mg	AUG1998 - 23SEP1998	U	U	Pneumonia staphylococcal, Rash, Pyrexia, Disseminated intravascular coagulation, Haemoglobin decreased, Platelet count decreased, Convulsion;	Resolved	Reporter considered symptoms of pneumonia, rash and fever not to be part of the hypersensitivity reaction. Concurrent valproate. On follow up patient found to have staphlococcal pneumonia. LTG re-started.
Investigations											
#B0024440A	UK	RA	1Y / F	TAB	70mg	U	(b) (6)	U	Liver function test abnormal, Coagulopathy, Epilepsy, Renal tubular necrosis;	Unresolved	-
Skin and subcutaneous tissue disorders											
#B0052916A	Croatia	LI	22M / M	TABU	2mgk	21DEC1996 - U	U	14D	Toxic epidermal necrolysis, Rash maculo-papular, Pyrexia, Malaise, Dehydration, Photodermatosis, Blister;	Resolved	Concurrent valproate. Start dose 10x recommended. TEN confirmed on biopsy. recovered fully after 4 weeks. Vukelic D. Lamotrigine & Toxic Epidermal Necrolysis. Dermatology 1997;195:307

Table 38 (Continued) **Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug**

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
#D0001501A	Germany	MD MR	19M / F	TAB	37.5mg	15SEP1997 - U	(b) (6)	34D	Stevens-Johnson syndrome, Rash, Pyrexia;	Resolved	Concurrent vigabatrin, clobazam. High dose of LTG. Rash with mucous membrane involvement, resolved in 14 days.
#D0002788A	Germany	MD	17M / M	TAB	U	12OCT1998 - U	(b) (6)	21D	Stevens-Johnson syndrome;	Resolved	Concurrent valproate. Treated with corticosteroids.
#A0606242A	Mexico	MD	1Y / F	U	U	U	U	U	Stevens-Johnson syndrome;	Unknown	-
#B0046698A	UK	MD	10M / M	U	U	U	U	U	Erythema multiforme;	Unknown	Treated in intensive care. No other details.
#A0557588A	United States	MD RP	7M / F	TABD	U	U	U	U	Stevens-Johnson syndrome;	Unknown	-

Table 38 (Continued) Line Listing of Sponsor's Post-Marketing Reports (Selection of Noteworthy Cases Determined by Reviewer) in Children < 24 Months with LAMOTRIGINE as Suspect Drug

Case No.	Country	Report Source	Age/ Sex	Form'n or Route	TDD	Treatment Dates*	Event Onset	TTO	Events	Outcome	Comments
#B0123299A	Mexico	MD	21M / F	TAB	0.5tab	03Sep2001 - 02Oct2001	(b) (6)	3W	Stevens-Johnson syndrome;	Fatal	-
#B0060512A	Switzerland	MD	22M / F	TAB	37.5mg	27AUG1998 - 01OCT1998		4W	Stevens-Johnson syndrome, Multi-organ failure, Rhabdomyolysis, Meningitis aseptic, Cardiovascular disorder, Generalised oedema, Hepatic enzyme abnormal, Coagulation test abnormal, CSF test abnormal, Liver disorder, Coagulopathy, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Blood albumin decreased, Blood creatine phosphokinase increased, Haemoglobin decreased, Blood fibrinogen decreased;	Improved	Concurrent valproate. Patient had raised LFTs and decreased fibrinogen prior to starting LTG. Examination ruled out toxic shock, bacterial sepsis or generalised herpes infection. No mention of rash despite diagnosis of SJS.

were receiving concomitant valproate and one concomitant vigabatrin and clonazepam. The case of toxic epidermal necrolysis was reported in a 22 month old child who was also receiving concurrent valproate.

Study 20007 (4 Month SafetyUpdate)

As part of the 4 Month Safety Update, the GSK Clinical Safety database was searched from 28 July 2006 up to 31 October 2006, to identify all post-marketing reports in children less than 24 months of age in which lamotrigine was reported as a suspect drug. (The data cut-off date for postmarketing data in NDA 20-241/S-032 and NDA 20-764/S-025 was 27 July 2006). A listing of post marketing reports in children less than 24 months of age was provided.

The search identified three serious AE reports; reported from United States, Netherlands and France. Two of these reports were received from consumers and one from the regulatory agency.

Deaths

None of the three reports concerned a fatal outcome.

Serious Adverse Events

Of the three SAE reports, two concerned the development of rash, and are described The report not documenting a rash, described a 2-year-old male patient, who was taking approximately 10 other medications for epilepsy including valproate and carbamazepine. Within the same month of starting lamotrigine the patient experienced increased seizures. The mother reported that she thought her son was taking a lamotrigine dose that was greater than that recommended for an adult. The patient had continued to take lamotrigine for one year. After an unspecified duration of lamotrigine treatment, the patient developed delays in development, learning problems and mood
changes.

Rash

Rash is an AE of special interest in the infant population as, during the early development of lamotrigine, **a higher incidence of both rash and serious rash was noted in pediatric subjects compared with adults**. There were two SAE reports that concerned the occurrence of rash following lamotrigine administration. The first report described a 2-year-old female patient, who was concurrently taking salbutamol, fluticasone, amoxicillin, phenethicillin and clobazam. After 11 days and 4 months of lamotrigine 5mg daily and valproate 360mg daily treatment, respectively, the patient developed Stevens-Johnson syndrome. The patient was treated with immunoglobulins. Treatment with lamotrigine, valproate, amoxicillin and phenethicillin were discontinued. The patient recovered.

The second report concerned a 1-year-old female patient, who was concurrently taking valproate and clonazepam. The patient started lamotrigine, dose not specified, and approximately 21 days later developed macular papular rash on face and mucous membranes. Lamotrigine was discontinued on the same day, and the patient was treated with betamethasone and mouth wash. Skin biopsy revealed mixed peri-capillaritis with leucocytoclasia. The patient recovered.

Reviewer Comments

- Review of the post-marketing experience by the sponsor showed several case of SAEs (including 4 death reflecting SAEs described in the lamotrigine label but not apparently observed in the sponsor's clinical development program which comprised 256 patients (1-24 months at onset of treatment) treated for various times including 189 treated for $\geq$ 6 months and 111 treated for $\geq$ 6 months. In particular, the clinical development program did not identify any cases of serious rash, multiorgan failure, disseminated

intravascular coagulation (DIC), serious hepatotoxicity, or serious blood dyscrasias. I did not observed such cases in the sponsor's narratives provided for SAEs and discontinuations for adverse events. In contrast, the sponsor's post-marketing presentation (see Table 38 for brief description of some cases) identified 10 cases of serious rash including SJS (7 cases with 1 fatal outcome), TEN (1), erythema multiforme (1), and rash showing mixed peri-capillaritis with leukocytoclasia (1). The outcome of 3 cases of serious rash (2 SJS and 1 erythema multiforme) are unknown. Other cases stimulating my interest in Table 38 are rhabdomyolysis (1), pancreatitis (1), DIC (2), blindness (1), and hepatotoxicity (described as abnormal hepatic dysfunction or "hepatic failure) including 2 cases with unresolved outcome.

The sponsor did not submit MedWatch forms for the post-marketing cases with the NDA. However, after in inquiry about some of the cases, the sponsor did recently submit MedWatch forms but at this late time in the review cycle, these MedWatch forms could not be carefully reviewed. A brief scanning of these reports suggested that in many instances the information provided seemed extremely limited.

Considering the "rule of 3," the "incidence cap" for not observing serious adverse reactions is ~ 1 % (3/256 individuals exposed). It is also not known, what is the extent of post-marketing exposure/use in this very young population? Although it is clearly recognized that patients ≤ 24 months are treated with lamotrigine, we do not have any estimate of what the use is and thus cannot calculate rates for certain serious adverse reactions. The sponsor did not provide any use estimates. Although I recently inquired (within the Agency) to obtain lamotrigine use data for patients 1-24 months and < 1 month, I have not yet received any information.

A serious question that arises is, why many serious adverse reaction cases identified in the post-marketing review were not identified in the clinical development program? I can think of 2 possible explanations, : 1) the exposure is relatively small and limited for observing certain serious outcomes that may be occurring an incidence of ≤ 1 %; or 2) the clinical development program was of such poor quality that it was not sufficiently sensitive for capturing and describing such serious adverse reactions. Although I find it difficult to entertain the latter possibility because it seems that it would seem unlikely and somewhat difficult to "miss" identifying cases of SJS, hepatic or multiorgran failure or DIC, this possibility cannot necessarily be excluded..

- The sponsor neglected to mention an additional death (described in the sponsor's line listing) of 23 month old boy who died with rhabdomyolysis, shock, pneumonia, acute pre-renal failure and dehydration. This patient (D0045625A) is shown in my abstraction and presentation of certain patients with SAEs in the sponsor's line listings.

- It is known and described in the lamotrigine label that the risk for experiencing serious rash in pediatric patients (2-16 years) is nearly 3 fold higher than that in adults. More specifically, this risk is considered to be approximately 0.8 % (8/1000) and approximately 0.3 %) in adults treated in the adjunctive epilepsy setting. This risk is also believed to be highest in the first 2 months of titrated treatment with lamotrigine but can also occur later. It is not known if the risk in this younger population (1-24 months) is similar to, greater, than, or less than that for older pediatric patients.

- I also inquired of Kate Phelan (ODS) to search AERs for adverse reactions associated with lamotrigine treatment in patients ≤ 24 months. The initial search revealed 225 reports, some of which included adverse

reactions related to in utero fetal exposure to lamotrigine from mothers using lamotrigine. Although another search of deaths in subjects < 2 years of age suggested that there were 22 deaths. However, it was not possible to know if there were any duplicated cases or if the exposure to lamotrigine had been post-natal instead of in utero. A follow-up search of line listings with narratives resulted in 130 pages of listed information. There was not sufficient time left in the review cycle to review this information in any serious depth. However, I did scan these listings to try to determine the apparent number of deaths that seemed to be related to post-natal exposure to lamotrigine. My search found 8 deaths (4 were also taking valproate-VPA) including :

- 24 month old female with abnormal liver function tests, renal failure, pyrexia, urticaria
- 24 month old male with rhabomyolysis, shock, pneumonia, acute pre-renal failure, dehydration
- 2 year old (gender unknown) death without details
- 23 month old male with hepatic function abnormal, purpura, cerebrovascular disorder
- 22 month old male with DIC, hepatic function abnormal, encephalopathy
- 17 month old male with apparent sudden death after a cold (history of intrauterine exposure to lamotrigine, ? not clear if also post-natal exposure)
- 15 month old female without any details of adverse reaction other than death
- 1 month old male with multiple congenital anomalies (? not clear if also post-natal exposure or if only history of intrauterine exposure to lamotrigine)

- I believe that 3 of the sponsor's 4 deaths (SJS case was not) are in the AERs database. Thus, it appears that there may be 9 post-marketing deaths that may have been associated with post-natal lamotrigine treatment. In addition, there are serious cases listed by the sponsor without known outcomes which could also have resulted in death. Thus, the number of post-marketing deaths may be even higher.

- The sponsor did not specify which cases that were discovered from the published literature.

- Several of the deaths (described by the sponsor or identified in AERs) appeared to occur within a few weeks of initiating treatment with lamotrigine. Thus, this close temporal relationship to lamotrigine exposure and suggests the possibility that the death was a result of lamotrigine treatment.

- (b) (4) **A detailed review of all AERs cases could further exacerbate concerns about SAEs (possibly expected from the label or new events not expected based upon the label) not observed in the sponsor's clinical development program.**

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 256 patients were exposed to lamotrigine in both trials (20006 and 20007) (Table 39). Long-term exposure of ≥ 26 weeks included 189 patients (110 with EIAED, 57 with nonEIDAED/"neutral" AED, 22 with

VPA). Long-term exposure of ≥ 52 weeks included 111 patients (73 with EIAED, 31 with nonEIDAED/"neutral" AED, 7 with VPA).

Table 39 Subject Disposition in All Studies (Safety Population: Studies LAM20006 and LAM20007- Combined)

	Number of Subjects						
	LAM20006 OLP	LAM20006 DBP		LAM20007			LAM20006 and LAM20007
	LTG	Placebo[b]	LTG[b]	LTG Experienced[c]	LTG Naive	Total	LTG
Total Exposures[a]	177	19	19	125	79	204	256

Data Source: Table 5.1
LTG=LAMICTAL
a. Entries are the number of unique subjects who received at least one dose of study drug within a study.
b. These subjects also received LAMICTAL during the OLP of LAM20006 prior to being randomized to the DBP.
c. Number of subjects exposed to LAMICTAL in LAM20007 who were also exposed to LAMICTAL in LAM20006.

Reviewer Comment

- My most important concern about exposure relates to the small number (total N = 38; 19/treatment group) of patients treated under randomized, double-blinded, placebo-controlled conditions for a relatively short period and after dose escalation and determination of tolerability to lamotrigine.

7.2.1.1 Study type and design/patient enumeration

Most of the long-term study exposure was obtained in open-label extension Study 20007 which enrolled patients treated with lamotrigine in Study 2006 and also patients naive to lamotrigine (Table 39).

7.2.1.2 Demographics

Both studies enrolled a reasonable number of males and females and a "reasonable" patients throughout the whole dose range of 1-24 months. It should be noted that although young infants aged 1-6 months were enrolled in the open-label portions of studies 20006 and 20007, the age sub-group of 1-6 months had the smallest proportion of patients in each study (16 % for study 20006 and 8 % of study 20007) vs older age sub-groups (32 % for age sub-group 6-12 months for study 20006 and 26 % of study 20007; 53 % for age sub-group 6-12 months for study 20006 and 67 % of study 20007) Thus, the majority of patients enrolled in both studies were relatively older patients > 12 months.

Reviewer Comment

- The percentage of patients enrolled was clearly the greatest in the highest age subgroup (> 12 months). The number (N = 1 < 6 months) enrolled in the randomized, double-blinded, placebo-controlled study phase was insufficient (b) (4) The number studied for safety in this youngest age subgroup is also probably insufficient to assess safety adequately. The number of patients studied in the middle age subgroup (6-12 months) is probably

reasonable for long-term safety considerations if the drug was shown to be effective for patients ≤ 24 months.

7.2.1.3 Extent of exposure (dose/duration)

Table 40 Long-Term Exposure of All Patients (Studies 20006 and 20007) by Modal Total Daily Dose of Lamotrigine and by Concomitant AED Class

	EIAED						NonEIAED				
Duration of Treatment (weeks)[1]	Number receiving dose (mg/kg/day)						Number receiving dose (mg/kg/day)				
	Total	<5	5-8	>8-11	>11-15	>15	Total	<2.5	2.5-<4.5	4.5-7.5	>7.5
>=26	110	9	20	16	31	34	57	9	7	29	12
>=52	73	5	12	8	22	26	31	5	3	13	10
>=78	12	1	3	1	1	6	4	0	0	2	2

	VPA				
Duration of Treatment (weeks)[1]	Number receiving dose (mg/kg/day)				
	Total	<1	1-3	>3-5	>5
>=26	22	2	4	8	8
>=52	7	0	2	2	3
>=78	1	0	1	0	0

Reviewer Comment

- The long-term safety experience is quite good for patients (age not specified) with EIAEDs or nonEIAEDs but relatively small for patients with VPA as a concomitant AED.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See section 7.1.17 Postmarketing Experience and section 8.6 Literature Review

7.2.2.1 Other studies

- Not applicable

7.2.2.2 Postmarketing experience

See section 7.1.17. Postmarketing Experience

7.2.2.3 Literature

See section 8.6 Literature Review

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- Not applicable

7.2.5 Adequacy of Routine Clinical Testing

- Not applicable

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

- Not applicable

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

Reviewer Comment

- My general impression of the quality and completeness of data was that I did not find that there were clear problems to make me suspicious of the quality and completeness of data. However, as noted by my many concerns outlined throughout my review, my overall impression was that quality of the analyses and the critical nature of the analyses were generally poor.

7.2.9 Additional Submissions, Including Safety Update

This 120-day Safety Update report updated the safety profile for LAMICTAL tablets as adjunctive or discontinued the study. No other studies were in progress or completed during the reporting period.

Sponsor's Summary and Conclusions Including Safety Update

A total of 206 subjects were enrolled into study 20007 and 204 subjects received study drug. There were no new exposures to study drug during the reporting period. Five additional subjects were exposed to lamotrigine for at least 48 weeks bringing the total number of subjects exposed to lamotrigine (LAM20006 and LAM20007 combined) for at least 48 weeks to 142 subjects.

This 120-day Safety Update report updated the safety profile for lamotrigine tablets as adjunctive therapy in the treatment of pediatric subjects (1-24 months of age) with partial seizures by summarizing information available since the cut-off date for safety information in NDA 20-241/S-032 and NDA 20-764/S (06 January 2006) through the cut-off date of 31 October 2006. This report includes updated safety information for study LAM20007 which completed during the reporting period. At the time of the interim analysis of study LAM20007 for NDA 20-241/S-032 and NDA 20-764/S-025, there were 20 subjects ongoing in the study. These subjects have since completed or discontinued the study. No other studies were in progress or completed during the reporting period.

Overall, 177 (87%) subjects experienced AEs. The AE with the highest incidence was pyrexia: 92 (45%) subjects. Overall, 19 (9%) subjects experienced AEs that were judged to be reasonably attributable to study drug. The AE with the highest incidence that was judged to be reasonably attributable to study drug was irritability: 10 (5%) subjects. Seven subjects died in both studies. None of the events was judged to be related to study medication. No additional subjects died during this reporting period. During the reporting period, there were four new SAEs reported for two subjects and updates to previously reported SAEs for four subjects. Overall, 70 (34%) subjects experienced SAEs including the seven subjects who died. Pneumonia, complex partial seizures and status epilepticus were among the most common (≥5%) SAEs reported during the study. One subject reported rash that was considered to be a SAE. Overall, 18 (9%) subjects were discontinued due to an AE. No additional subjects withdrew from the study due to an AE during the reporting period.

The nature and frequency of AEs were similar to those previously reported in NDA 20-241/S-032 and NDA 20-764/S-025.

The sponsor thought that the additional data from study LAM20007 continues to support the conclusions reached in NDA 20-241/S-032 and NDA 20-764/S-025, that the LAMICTAL continues to have an acceptable safety and tolerability profile in this population, (b) (4) submitted as part of NDA 20-241/S-032 and NDA 20-764/S-025.

Reviewer Comment

- The Safety Update appeared to have 6 patients with SAEs, none of which seemed noteworthy deserving comment. I agree that the Safety Update did not suggest any difference in my impression of the safety profile for this population compared to my review of the data prior to the Safety Update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Reviewer Comment

- The absence of randomized, double-blind, placebo-controlled study data for unselected patients and the empirically collected safety data during the titration/dose-escalation period made it difficult to assess the true drug-related adverse events or other findings.

- The collection of safety data during the relatively brief randomized, double-blind, placebo-controlled study withdrawal period was not very useful for reflecting a placebo-controlled experience relative to lamotrigine treatment because these patients had already been selected to a certain extent based upon their tolerability to lamotrigine and a specific tolerable dosing regimen.

- I have outlined in more detail in section 7.1 (Methods and Findings) many of my concerns about the important limitations of the safety data and their analyses and have more briefly reviewed these in my conclusions shown below here.

Reviewer Safety Conclusions

- I conclude that there are 3 major problems/concerns with the regard to the safety data (b) (4) (see section 7 Integrated Review of Safety and section 7.1 Methods and Findings).

    - The small number of randomized patients (19/treatment group) and study design (randomized withdrawal) in the relatively brief (up to 8 weeks, and frequently much less for many patients) placebo-controlled study phase and short did not facilitate collection of useful safety data.

    - The sponsor did not adequately collect adverse event data that might reflect adverse reactions related to symptoms which were not able to be communicated in this very young population.

    - The sponsor's coding and analyses of adverse events appeared to be of poor quality and did not seem to provide a reliable assessment of not only the frequency of certain adverse event safety data but also the nature/type of certain adverse events.

- There were no placebo-controlled safety data collected during the titration phase. Treatment during the titration phase is frequently not only associated with the development of many adverse events but also adverse events of greater frequency and possibly even greater severity than adverse events that can develop in the maintenance period after maximal lamotrigine titration has occurred and the patient had demonstrated tolerability.

- The vast majority of safety data collected resulted from open-label treatment which typically significantly underestimates the frequency of adverse events. Long-term, open-label data are particularly helpful in characterizing more uncommon or rare adverse reactions to treatment and do not substitute for placebo-controlled safety data.

- The absence of placebo-controlled safety data during the lamotrigine titration phase in an unselected population did not allow one to characterize the basic safety profile of lamotrigine for this young population. Comparison of placebo-controlled safety data (i.e. placebo vs drug treatment) is the main method by which we assess the basic safety profile of a drug for treatment of a certain, unselected population.

- There was no attempt to characterize dose-response (b) (4) There was no attempt/consideration to characterize dose-response by randomizing patients to more than one fixed lamotrigine dose. (b) (4)

- The sponsor did not provide any adverse event analyses during the titration vs the maintenance phases in the open-label experience. Such analyses might show an increased frequency of adverse events developing during the titration phase.

- The safety data collected during the randomized, withdrawal placebo-controlled phase seems to be of limited value because this brief treatment phase (ranging from a few days to a maximum of 8 weeks) captures safety data after patients have been treated with a tolerable lamotrigine dose and frequently have already experienced adverse events previously while being titrated and maintained on a seemingly therapeutic and tolerable lamotrigine dose.

- There was no collection of blood pressure data in this very young population. Lamotrigine has the potential (as does any CNS acting drug) to alter blood pressure (especially lower blood pressure). Given this possibility and that the significant frequency of "dizziness" (which I do not think can exclude a decrease in blood pressure in at least some lamotrigine treated patients) observed in older pediatric patients (and adults), it is conceivable that lamotrigine could be exerting significant effects on blood pressure, an important vital sign parameter that was not collected (for unknown reasons). Although the lamotrigine label does not describe effects on blood pressure, I am not confident that data have been adequately collected and analyzed to demonstrate or exclude effects on blood pressure (especially related to changes of position and time of dosing). I cannot think of a good reason why blood pressure was not measured and collected throughout these studies. Furthermore, normative data exist for this very young population.

(b) (4)

(b) (4)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor pooled many safety data (including TEAEs, VS, ECG, and clinical laboratory data) that was virtually all derived from open-label treatment from both studies 20006 and 20007.

Reviewer Comment

- I did not think that pooling all these data (primarily open-label) was very helpful in providing any insight compared to that obtained from review the studies separately.

7.4.1.1 Pooled data vs. individual study data

See Reviewer Comment for section 7.4.1.

7.4.1.2 Combining data

See Reviewer Comment for section 7.4.1.

7.4.2 Explorations for Predictive Factors

- Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

Reviewer Comment

- The sponsor did not conduct analyses assessing for dose-dependent AE findings of lamotrigine associated with different dosing per se but did conduct analyses according to various dosing regimens based upon the class of concomitant AED and also the dose of lamotrigine within each class of concomitant.

  The sponsor did not assess dose-dependent effects of lamotrigine by randomizing patients to different fixed doses of lamotrigine vs placebo. This approach would have been the best means of assessing any dose-dependent effects of lamotrigine.

  I did not think that any of the sponsor explorations of dose-dependent effects of lamotrigine provided any useful information.

7.4.2.2 Explorations for time dependency for adverse findings

Reviewer Comment

- The sponsor did not conduct any exploratory analyses assessing for time-dependent effects of lamotrigine. In particular, I believe that it would have been desirable and potentially more insightful to explore analyses of the safety data (especially TEAEs) according to the time of onset of TEAEs (e.g. lamotrigine titration phase or maintenance phase) and whether TEAEs with onset in the titration phase persisted into the maintenance phase.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor conducted pooled exploratory analyses of the most common TEAEs by various subgroups including age, gender, and race.

Reviewer Comment

- These pooled analyses of mostly open-label data from both studies did not provide any useful information with the following exceptions that I thought were worthy of mention. There were some notable differences in the incidence of constipation (< 6 months-28 %, 6-12 months-12 %, > 12-24 months-17 %) and pneumonia (< 6 months-28 %, 6-12 months-9%, > 12-24 months-10 %) with the greatest frequency occurring in the youngest age subgroup (, 6 months). In contrast, the incidence of diarrhea appeared to increase progressively with age (< 6 months-3 %, 6-12 months-10 %, > 12-24 months-16 %).

7.4.2.4 Explorations for drug-disease interactions

Reviewer Comment

- The sponsor did not conduct exploratory analyses for drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

Reviewer Comment

- The sponsor did conduct exploratory analyses for drug-drug interactions based upon the class type of concomitant AED (e.g. EI, nonEI/"neutral", or VPA). I did not find any noteworthy findings for these analyses relative to TEAEs.

7.4.3 Causality Determination

In the Clinical Overview, the sponsor noted that 18 % of patients (from both studies) experienced TEAEs that were judged to be "reasonably attributable to study drug by the investigator." The following TEAEs (irritability-8 %, any type seizure-4 %, any rash-4 %, somnolence-3 %, constipation-2 %, insomnia-2 %, tremor-2 %, ataxia-1 %, lethargy-1 %, vomiting-1%, decreased appetite-1 %) represent the most common ($\geq$ 1 %)TEAEs considered possibly caused by lamotrigine treatment.

Reviewer Comment

- It is difficult to consider how reliable this attribution based upon clinical investigator judgment, mainly during open-label treatment may be. A much better way to have insight into causality is from an adequate study duration exposure/treatment of unselected patients in a randomized, double-blind, placebo-controlled study observation. Comparison of the frequency of any adverse reaction associated with lamotrigine treatment with the frequency of placebo treatment is probably a more useful way to assess causality. Another excellent way to consider causality is from "rechallenge" experience. However, I did not note any descriptions by the sponsor in which an adverse reaction was associated with a "rechallenge" experience.

  The collection of safety data during the relatively brief randomized, double-blind, placebo-controlled study withdrawal period was not very useful for reflecting a placebo-controlled experience relative to lamotrigine treatment because these patients had already been selected to a certain extent based upon their tolerability to lamotrigine and a specific tolerable dosing regimen.

  I also think that the frequency reported by the sponsor as per investigators' judgments to be caused possibly by lamotrigine would be much higher overall (for lamotrigine- and placebo-treated infants/toddlers) and also in favor of lamotrigine (over placebo) if data were derived from randomized, double-blind, placebo-controlled study of unselected patients titrated and maintained on lamotrigine vs placebo

- It is of interest that many of these TEAEs thought to be caused by lamotrigine by investigators would also be considered to caused (possibly) by lamotrigine by me. I also note that many of these TEAEs potentially reflect altered/"abnormal" behaviors (e.g. irritability, decreased feeding/eating, difficulty sleeping, difficulty walking) that I have suggested (see section 7..1.5.1 Eliciting adverse events in the development program) may be more non-specific TEAEs reflecting other TEAEs that are not able to be communicated adequately by these very young patients.

- It is also of interest that lethargy and somnolence (which are potentially reasonably expected adverse reactions) have occurred and have been "split" into separate categories but may really be the same adverse reaction captured/coded differently and with distinction when in fact there may not be any real distinction between these 2 different PTs.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Patitents were dosed according to the following titration/dose escalation and maintenance regimens based upon weight and the type/class of concomitant AEDs.

- LTG added to VPA or non-EIAEDs
  Week 1 and 2: 0.15mg/kg/day
  Week 3 and 4: 0.3mg/kg/day

Maximum maintenance dose: 5.1 mg/kg/day or 200 mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 0.3 mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

- LTG added to EIAEDs (maximum of two)
  Week 1 and 2: 0.6mg/kg/day
  Week 3 and 4: 1.2mg/kg/day

Once the maintenance dose was reached, subjects in the efficacy study LAM20006 who had a ≥ 40% reduction from baseline seizure frequency during the last 28 days of that optimization period were randomized (1:1) to continued lamotrigine treatment or to a gradual, blinding withdrawal to placebo during the double blind phase (DBP) and remained in the DBP until one of the escape criteria was met.

The subjects in the safety study (LAM20007) were treated with the same dosing regimens and ideally were to have remained on an optimized dose of lamotrigine for at least 48 weeks, to assess safety and tolerability and to assess effect of 48 weeks of lamotrigine on seizure frequency.

(b) (4)

Reviewer Comment

(b) (4)

(b) (4)

8.2 Drug-Drug Interactions

The sponsor conducted many various analyses related to concomitant AEDs according to three classes (EI AEDs that lower plasma lamotrigine levels , nonEI/"neutral AEDs that do not significantly alter plasma lamotrigine levels, VPA that increases plasma lamotrigine levels).

Reviewer Comment

- When appropriate/relevant, I have made any noteworthy comments about drug-drug- interactions primarily considering concomitant AEDs (i.e. the 3 classes of AEDs outlined above). The Clinical Pharmacology review provides more detailed information about drug-drug interactions in these infants with regard to concomitant AEDs. The sponsor did not provide any other information about drug-drug interactions other than how concomitant AEDs influenced plasma lamotrigine levels in these young pediatric patients studied.

8.3 Special Populations

Reviewer Comment

- There were no special populations studied other than the primary one of very young infants/toddlers (1-24 months).

8.4 Pediatrics

Reviewer Comment

- This sNDA is related to a PWR (see section 2.5 Presubmission Regulatory Activity that outlines information chronologically related to the PWR. This PWR sNDA was presented to the Agency Pediatric Exclusivity Board on 2/14/07 and pediatric exclusivity was granted by the Board because it was determined that the terms of the PWR had technically been met by the sponsor.

8.5 Advisory Committee Meeting

Reviewer Comment

- There are no plans for an Advisory Committee meeting because there is no perceived need for one at this time.

8.5 Literature Review

Reviewer Comment

- The sponsor did not conduct a comprehensive search of the published literature seeking information related to efficacy, safety, or PK of pediatric patients 1-24 months of age. The sponsor did provide lists of published references, particularly in the section on Post-Marketing but as I had pointed out, did not specify which publications supported any specific comments, In summary, a comprehensive search of the published literature that should have been conducted, discussed, and submitted was not provided by the sponsor.

8.7 Postmarketing Risk Management Plan

- Not applicable (b) (4)

8.8 Other Relevant Materials

- Not applicable

9. OVERALL ASSESSMENT

9.1 Conclusions

Reviewer Efficacy Conclusions

(b) (4)

- Based upon the primary efficacy analysis of the ITT population (confirm by our Statistical Review by Dr. Sharon Yan, ostensibly, this is a failed study which is not statistically significant ($p = 0.0737$ for chi-square statistic which may not be appropriate because of small sample size; $p = 0.151$ for Fisher's exact test which may be more appropriate). In agreement with this view, the sponsor acknowledges that the difference in treatment failures for the ITT analysis of the randomized phase did not achieve statistical significance ($p = 0.07$).

- Overall, my numerous concerns outlined in my Reviewer Comments about the study design, conduct, and analysis of the controlled trial phase of study 20006 do not allow me to have confidence in any primary efficacy result of this study, even if the ostensible p value reported by the sponsor was < 0.05.

(b) (4)

(b) (4)

- I am concerned about the relatively small number of patients studied in the randomized, placebo-controlled study phase (19 patients/treatment group of lamotrigine or placebo) which does not seem to facilitate the collection of robust/reliable data.

(b) (4)

Reviewer Safety Conclusions

- I conclude that there are 3 major problems/concerns with the regard to the safety data (b) (4) (see section 7 Integrated Review of Safety and section 7.1 Methods and Findings).

    - The small number of randomized patients (19/treatment group) and study design (randomized withdrawal) in the relatively brief (up to 8 weeks, and frequently much less for many patients) placebo-controlled study phase and short did not facilitate collection of useful safety data.

- The sponsor did not adequately collect adverse event data that might reflect adverse reactions related to symptoms which were not able to be communicated in this very young population.

- The sponsor's coding and analyses of adverse events appeared to be of poor quality and did not seem to provide a reliable assessment of not only the frequency of certain adverse event safety data but also the nature/type of certain adverse events.

- There were no placebo-controlled safety data collected during the titration phase. Treatment during the titration phase is frequently not only associated with the development of many adverse events but also adverse events of greater frequency and possibly even greater severity than adverse events that can develop in the maintenance period after maximal lamotrigine titration has occurred and the patient had demonstrated tolerability.

- The vast majority of safety data collected resulted from open-label treatment which typically significantly underestimates the frequency of adverse events. Long-term, open-label data are particularly helpful in characterizing more uncommon or rare adverse reactions to treatment and do not substitute for placebo-controlled safety data.

- The absence of placebo-controlled safety data during the lamotrigine titration phase in an unselected population did not allow one to characterize the basic safety profile of lamotrigine for this young population. Comparison of placebo-controlled safety data (i.e. placebo vs drug treatment) is the main method by which we assess the basic safety profile of a drug for treatment of a certain, unselected population.

- There was no attempt to characterize dose-response (b) (4) [redacted] There was no attempt/consideration to characterize dose-response by randomizing patients to more than one fixed lamotrigine dose (b) (4) [redacted]

- The sponsor did not provide any adverse event analyses during the titration vs the maintenance phases in the open-label experience. Such analyses might show an increased frequency of adverse events developing during the titration phase.

- The safety data collected during the randomized, withdrawal placebo-controlled phase seems to be of limited value because this brief treatment phase (ranging from a few days to a maximum of 8 weeks) captures safety data after patients have been treated with a tolerable lamotrigine dose and frequently have already experienced adverse events previously while being titrated and maintained on a seemingly therapeutic and tolerable lamotrigine dose.

- There was no collection of blood pressure data in this very young population. Lamotrigine has the potential (as does any CNS acting drug) to alter blood pressure (especially lower blood pressure). Given this possibility and that the significant frequency of "dizziness" (which I do not think can exclude a decrease in

blood pressure in at least some lamotrigine treated patients) observed in older pediatric patients (and adults), it is conceivable that lamotrigine could be exerting significant effects on blood pressure, an important vital sign parameter that was not collected (for unknown reasons). Although the lamotrigine label does not describe effects on blood pressure, I am not confident that data have been adequately collected and analyzed to demonstrate or exclude effects on blood pressure (especially related to changes of position and time of dosing). I cannot think of a good reason why blood pressure was not measured and collected throughout these studies. Furthermore, normative data exist for this very young population.

(b) (4)

9.2 Recommendation on Regulatory Action

- Not applicable (b) (4)

9.3 Recommendation on Postmarketing Actions

- Not applicable (b) (4)

9.3.1 Risk Management Activity

- Not applicable (b) (4)

9.3.2 Required Phase 4 Commitments

- Not applicable (b) (4)

9.3.3 Other Phase 4 Requests

- Not applicable (b) (4)

9.4 (b) (4)

Reviewer Comment

- (b) (4)

9.5 Comments to Applicant

Reviewer Comment

- Major comments to the sponsor derived from my efficacy and safety conclusions are recommended (b) (4)

10. APPENDICES

- Not applicable

10.1 Review of Individual Study Reports

- Not applicable

10.2 Line-by-Line Labeling Review

Not applicable (b) (4)

REFERENCES

- Not applicable

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

/s/

Leonard Kapcala
6/14/2007 06:41:09 PM
MEDICAL OFFICER

John, Here is my review that has been finalized. You've seen most of this including all substantive info and my efficacy and safety conclusions. Please sign and let me know if any questions.
Thanx. Len

John Feeney
6/15/2007 01:36:18 PM
MEDICAL OFFICER

(b) (4)

See my supervisory review.