Table 4. Prospective Registry - Antiepileptic Drug Polytherapy Exposure in Pregnancy, by Trimester of Exposure and Outcome (continued)

1 September 1992 - 30 September 1997

Second-Trimester Exposures: Concomitant Antiepileptic Drug Exposures	Outcomes with Birth Defects	Outcomes without Reported Birth Defects[a]: Live Births Without Defects	Spontaneous Pregnancy Losses/Fetal Deaths	Induced Abortions	Total
valproate	0	1	0	0	1
Total	0	1	0	0	1

Table 5. Retrospective Reports - Lamotrigine Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure
1 September 1992 - 30 September 1997

First-Trimester Lamotrigine Polytherapy Exposure:

Case Report #		Exposure	Date of Report	Infant Sex	Gestational Weeks at Outcome	Outcome
2608	28	Lamotrigine 200 mg/day from week 0-19 Valproic acid preconception and throughout pregnancy.	1 Sept 92	Unknown	19	Induced abortion following U/S detection of neural tube defects. Spina bifida with meningocele, hydrocephalus and cerebellar deformity; "lemon-shaped head and banana-shaped cerebellum with hydrocephalus.
2635	27	Lamotrigine 200 mg/day for weeks 0-39 Carbamazepine preconception throughout pregnancy.	22 Oct 93	F	39	Live infant with choanal atresia; stenosis later perforated.
2641	22	Lamotrigine 200 mg/day from week 0-35 Carbamazepine preconception throughout pregnancy.	23 Feb 94	M	35	Live infant reported as having "Congenital teratogenic face" with hypertelorism, downturned mouth, epicanthal folds, flattened nasal tip, micrognathia, slight bitemporal narrowing and marked hirsutes; has had "jittery hypotonicity." At time of follow-up, reported to have developmental delay (functioning at a 3-month-old level at 6 months of age).
2688	33	Lamotrigine 400 mg/day from week 0-6 Amitriptyline preconception throughout pregnancy.	31 Aug 95	Unknown	Unknown	Live infant described as "abnormal," no details provided.

Table 5. Retrospective Reports - Lamotrigine Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure
1 September 1992 - 30 September 1997

First-Trimester Lamotrigine Polytherapy Exposure:

Case Report #		Exposure	Date of Report	Infant Sex	Gestational Weeks at Outcome	Outcome
2691	Unknown	Lamotrigine ? mg/day from week ? Valproate preconception throughout pregnancy.	6 Nov 95	Unknown	Unknown	Stillbirth. Multiple abnormalities including hydrocephalus.
3389	37	Lamotrigine 200 mg/day week 0-6 Carbamazepine throughout pregnancy.	9 Apr 96	M	32	Live infant with multiple congenital abnormalities described as: congenital cataracts, double outlet right ventricle, pulmonary atresia, high membranous ventricular septal defect, right sided arch, anorectal agenesis without fistula, abnormal rotation of the large intestine, tracheal agenesis/laryngeal agenesis, bronchi arising from esophagus, abnormal lobar formation of the right lung, ambiguous genitalia, testes in high intraabdominal position, abnormal twisted left ribs, sacral dysgenesis with hypoplasia and abnormal segmentation, hypertelorism, down sloping palpebral fissues.[g]
3887	Unknown	Lamotrigine and gabapentin doses/timing unknown	21 Jan 97	Unknown	Unknown	Live infant with no left auditory canal.

[3] Folic acid supplementation was not initiated until gestation week 11.
[g] Infant is 1 of a set of twins.

Table 5. Retrospective Reports - Lamotrigine Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure (continued)
1 September 1992 - 30 September 1997

First-Trimester Lamotrigine Monotherapy Exposure:

Case Report #	Maternal Age	Exposure	Date of Report	Infant Sex	Gestational Weeks at Outcome	Outcome
2694	32	Lamotrigine 300 mg/day from week ? 400 mg/day, from week ? 400 mg/day from week ?	11 Nov 95	M	26	Live infant with polydactyly, talipes ankle joints), dysmorphic features. Normal chromosome analysis.
*4161	33	Lamotrigine 150 mg/day from week 0-?	22 Apr 97	?	20	Induced abortion following diagnosis of anencephaly by ultrasound at 18 weeks gestation.
*4323	26	Lamotrigine 200 mg/day from week 0	24 Sep 96	?	?	Live infant born with stiff hands/wrists, mild contractures needing physiotherapy; reaction started when infant was 6 weeks old.
*4325	31	Lamotrigine 50 mg/day from week 0-35 and 125 mg/day from week 35-40	8 Jul 96	M	40	Live infant with eyes slightly upturned with minor epicanthal folds. High and narrow forehead, premature fusion of metopic sutures. Small for gestational age at birth.
*4548	31	Lamotrigine 200 mg/day from week 0-40	10 Sep 97	F	40	Live infant with left renal cysts; left kidney without function. No information on whether this was detected on ultrasound or after birth.
3028	36	Lamotrigine 50 mg/day week 2 100 mg/day from week 4 50 mg/day from week 6 Felbamate throughout pregnancy.	03/15/96	F	34	Live infant with fetal hydrops and chylothorax. NICU care, mechanical ventilation, BP support, diuretics, problems with lung development and kidney failure.
3390	35	Lamotrigine 200 mg/day from week 0-6	19 Feb 96	M	Unknown	Live infant reported to have head circumference above the 97th percentile. Skull x-rays revealed sagittal synostosis.[h]

[h] Surgery was performed and the reporting physician commented that the infant had "done extremely well since with no other developmental sequelae."

* Indicates new case since last report

TABLE 1 INCIDENCE OF RASH IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	453	64 (14.1%)	28 (6.2%)	0 (0.0%)	0 (0.0%)
ADJ/EIAED	302	25 (8.3%)	12 (4.0%)	3 (1.0%)	2 (0.7%)
ADJ/VPA	112	25 (22.3%)	14 (12.5%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	868	114 (13.1%)	54 (6.2%)	3 (0.3%)	2 (0.2%)

INITIAL MONO = initial monotherapy with LAMICTAL
ADJ/EIAED = LAMICTAL given as adjunctive therapy with EIAED prior to withdrawal of EIAED to achieve monotherapy with LAMICTAL
ADJ/VPA = LAMICTAL given as adjunctive therapy with VPA prior to withdrawal of VPA to achieve monotherapy with LAMICTAL
ADJ/OTHER = LAMICTAL given as adjunctive therapy with non-inhibiting/non-inducing AED prior to withdrawal of non-inhibiting/non-inducing AED to achieve monotherapy with LAMICTAL
Rash DC = rash leading to discontinuation of LAMICTAL
Hospitalized =rash associated with hospitalization

TABLE 2 INCIDENCE OF RASH FOR PATIENTS RECEIVING INCORRECT DOSING IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	272	54 (19.9%)	26 (9.6%)	0 (0%)	0 (0%)
ADJ/EIAED	173	18 (10.4%)	10 (5.8%)	2 (1.2%)	1 (0.6%)
ADJ/VPA	72	21 (29.2%)	13 (18.1%)	0 (0%)	0 (0%)
ADJ/OTHER	0				
TOTAL	517	93 (18.0%)	49 (9.5%)	2 (0.4%)	1 (0.2%)

TABLE 3 INCIDENCE OF RASH FOR PATIENTS RECEIVING CORRECT DOSING IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	181	10 (5.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
ADJ/EIAED	129	7 (5.4%)	2 (1.6%)	1 (0.8%)	1 (0.8%)
ADJ/VPA	40	4 (10.0%)	1(2.5%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	351	21 (6.0%)	5 (1.4%)	1 (0.3%)	1 (0.3%)

TABLE 4 INCIDENCE OF RASH IN COMPLETED DOUBLE-BLIND, ACTIVE COMPARATOR, INITIAL MONOTHERAPY STUDIES (See Tables S9, S10, Appendix 2)

AED	N	Rash	Rash DC	Hospitalized	Possible SJS
LAMICTAL	216	49 (23%)	22 (10%)	0 (0.0%)	0 (0.0%)
Carbamazepine	128	28 (22%)	27 (13%)	1 (0.7%)	0 (0.0%)
Phenytoin	95	10 (11%).	5 (5%)	0 (0.0%)	0 (0.0%)

TABLE 5 INCIDENCE OF RASH IN ALL COMPLETED ACTIVE COMPARATOR STUDIES UTILIZING MONOTHERAPY (See Tables 8.33 and 8.52 in Integrated Summary of Safety (ISS) for NDA 20-241/s-02)

AED	N	Rash	Rash DC	Hospitalized	Possible SJS
LAMICTAL	446	64 (14%)	27 (6%)	0 (0%)	0 (0%)
Carbamazepine	247	38 (15%)	23 (9%)	1 (0.4%)	0 (0.0%)
Phenytoin	95	10 (11%)	5 (5%)	0 (0%)	0 (0%)

TABLE 6 INCIDENCE OF RASH DURING THE ADJUNCTIVE PHASE OF COMPLETED MONOTHERAPY TRIALS (See Tables S4, S5, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
ADJ/EIAED	302	21 (7.0%)	11 (3.6%)	2 (0.7%)	1 (0.3%)
ADJ/VPA	112	24 (21.4%)	13 (11.6%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	415	46 (11.1%)	25 (6.0%)	2 (0.5%)	1 (0.2%)

TABLE 7 EFFECT OF INCORRECT DOSING ON THE INCIDENCE OF RASH DURING THE ADJUNCTIVE PHASE OF COMPLETED MONOTHERAPY TRIALS (See Tables S4, S5, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
ADJ/EIAED	173	16 (9.2%)	9 (5.2%)	2 (1.1%)	1 (0.6%)
ADJ/VPA	72	20 (27.8%)	12 (16.7%)	0 (0%)	0 (0%)
ADJ/OTHER	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	245	36 (14.7%)	22 (9.0%)	2 (0.8%)	1 (0.4%)

TABLE 8 EFFECT OF CORRECT DOSING ON THE INCIDENCE OF RASH DURING THE ADJUNCTIVE PHASE OF COMPLETED MONOTHERAPY TRIALS (See Tables S4, S5, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
ADJ/EIAED	129	5 (3.9%)	2 (1.6%)	0 (0.0%)	0 (0.0%)
ADJ/VPA	40	4 (10%)	1 (2.5%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	170	9 (5.3%)	3 (1.8%)	0 (0.0%)	0 (0.0%)

TABLE 1 INCIDENCE OF RASH IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	453	64 (14.1%)	28 (6.2%)	0 (0.0%)	0 (0.0%)
ADJ/EIAED	302	25 (8.3%)	12 (4.0%)	3 (1.0%)	2 (0.7%)
ADJ/VPA	112	25 (22.3%)	14 (12.5%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	868	114 (13.1%)	54 (6.2%)	3 (0.3%)	2 (0.2%)

INITIAL MONO = initial monotherapy with LAMICTAL
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ADJ/OTHER = LAMICTAL given as adjunctive therapy with non-inhibiting/non-inducing AED prior to withdrawal of non-inhibiting/non-inducing AED to achieve monotherapy with LAMICTAL
Rash DC = rash leading to discontinuation of LAMICTAL
Hospitalized =rash associated with hospitalization

TABLE 2 INCIDENCE OF RASH FOR PATIENTS RECEIVING INCORRECT DOSING IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	272	54 (19.9%)	26 (9.6%)	0 (0%)	0 (0%)
ADJ/EIAED	173	18 (10.4%)	10 (5.8%)	2 (1.2%)	1 (0.6%)
ADJ/VPA	72	21 (29.2%)	13 (18.1%)	0 (0%)	0 (0%)
ADJ/OTHER	0				
TOTAL	517	93 (18.0%)	49 (9.5%)	2 (0.4%)	1 (0.2%)

TABLE 3 INCIDENCE OF RASH FOR PATIENTS RECEIVING CORRECT DOSING IN COMPLETED MONOTHERAPY STUDIES (See Table S2, Appendix 2)

STUDY DESIGN	N	Rash	Rash DC	Hospitalized	Possible SJS
INITIAL MONO	181	10 (5.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
ADJ/EIAED	129	7 (5.4%)	2 (1.6%)	1 (0.8%)	1 (0.8%)
ADJ/VPA	40	4 (10.0%)	1(2.5%)	0 (0%)	0 (0%)
ADJ/OTHER	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	351	21 (6.0%)	5 (1.4%)	1 (0.3%)	1 (0.3%)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20,241 Supplement
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	Glaxo Wellcome, Inc.
Indication	Monotherapy of Partial Seizures in Adults
Correspondence Date	24 February 1997
Original Receipt Date	25 February 1997
Medical officer review completed	15 December 1997
New patient review	3 February 1998

Following are patients from monotherapy trial US30/31 who have been reclassified as escapers for the purposes of statistical reassessment:

30-1-01038 (LTG) - met criteria for doubling the highest 2-day seizure frequency (3/16-17/95).

31-6-06046 (LTG) - met criteria for doubling the highest 4-week seizure frequency (4/30-5/30/95).

31-17-17041 (LTG) - inadequate documention of seizures diaries (missing data, 1/6-25/95).

31-17-17032 (LTG) - consent withdrawal: per available medical documentation, the patient was "still having seizures, wants to try something else."

31-14-14055 (LTG) - protocol violation: per available medical documentation, the patient "verbally" reported a seizure count but did not keep a diary.

31-21-21177 (VPA) - protocol violation, but also met the highest 2-day seizure rate multiple times. (To meet escape criteria, this patient needed to have 2 seizures over a 2-day period. From 3/10-18/96, the patient had 1 seizure per day and also had 2 seizures over the 2-day periods of 3/31-4/1/96 and 4/12-4/13/96).

NOTE: This list, compiled in association with Dr. Sue-Jane Wang (Biometrics), is based on new data from the 2/2/98 telecon with the sponsor. It therefore supercedes information presented in the medical review of the supplemental NDA.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,241Supplement (Monotherapy) div file/Katz R/Ware J/Tresley R/3 February 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

COPY

ADDENDUM TO NDA REVIEW

NDA Number	20,241
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	Glaxo Wellcome, Inc.
Indication	Monotherapy of Partial Seizures in Adults (Supplemental NDA)
Correspondence Date	16 December 1998
Original NDA Receipt Date	24 February 1997
Review Completed	7 January 1998 (revised 2/2/98, per phone conversation with Betty McConnell, Glaxo-Wellcome)

On December 2 and 11, 1997, the Agency requested additional information regarding exposure data for the clinical trials presented in the ISS, along with summaries for all patients with rash and hospitalized rash. Additional information was also requested on three patients in one trial (UK124) that was, at the time of the NDA, still blinded. The present submission is a response to these requests.

The sponsor states that, "In reviewing our database, we noted that there were inconsistencies in the demographic information between the database and the information presented in the final study reports submitted with the supplement. . . .There is also an additional patient listed (105-5702; progressive immunosuppression and Lyell's syndrome [=TEN]) that was not summarized in the supplement" (introductory letter, v 45.1, p 2).

I have added data from the pivotal study (US30/31) to the new information, along with two patients listed in the NDA but not in the new submission (UK74: patients 74-1-5011 and 74-1-1120), and have prepared a new estimate of the incidences for rash in general and hospitalized rash. One study (Finland 514-94) has, however, been excluded since it is ongoing and still blinded.

For a total patient population of 1929 (NDA studies), there were 35 cases of rash, or a rate of 2%. Of these, eight patients had a hospitalized rash (8/1929, or 0.4%), including Stevens-Johnson and TEN.

In the pivotal study (US30/31), the rate for rash in general was 10/75 (13%), and for hospitalized rash 2/75 (2.7%, one of which was a case diagnosed as Stevens-Johnson). (These numbers were verified, 2/2/98, in a phone conversation with Betty McConnell, Glaxo-Wellsome.)

The rate for hospitalized rash, then, ranges from a low of 8/1929 (population base of all studies in the NDA, including the unblinded and uncontrolled) to a high of 2/75 (if the pivotal study US30/31 is considered by itself).

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,241Supplement (Monotherapy) div file/Katz R/Ware J/Tresley R/7 January 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20,241
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	Glaxo Wellcome, Inc.
Indication	Monotherapy of Partial Seizures in Adults (Supplemental NDA)
Classification	S
Correspondence Date	24 February 1997
Original Receipt Date	25 February 1997
Clinical Reviewer	Richard M. Tresley, MD
Review Completed	15 December 1997

CONTENTS

I. INTRODUCTION

Lamictal (LTG) was approved as adjunctive therapy in the treatment of partial seizures in adults with epilepsy on 27 December 1994. The sponsor has submitted a supplemental NDA, centering on the single pivotal trial US30/31, to support the indication for use of Lamictal as monotherapy to treat partial seizures in adults (≥13 years of age).

The present submission provides information about the 27 studies involved in the sponsor's LTG monotherapy program:

Table 3.1. Categorization of Clinical Studies for Monotherapy sNDA

Completed Monotherapy Studies in Epilepsy				Ongoing Monotherapy And Add-On Studies in Epilepsy	Monotherapy Studies Conducted by Local Operating Companies	Monotherapy Study in Migraine
Controlled		Uncontrolled				
Pivotal	Initial Monotherapy	Conversion to Monotherapy	Continuation Studies			
US 30/31	UK 49 UK 89 UK 74 UK 106	UK 105	UK 111 UK 115 UK 112	US 09, US 10, US 15, US 17 UK 87, UK 88 UK 58, UK 85 US 29[a] US 801[a] UK 126[a] UK 136[a] UK 124[a] UK 133[a]	UK 514 UK 1006 UK 405	UK 78
Data are fully reported. All AEs are summarized in Integrated Safety Summary. Final Study Reports are submitted.				Deaths, SAEs, and AEs leading to discontinuation for patients who received LAMICTAL monotherapy are provided in listings No Final Study Reports are submitted	Deaths, SAEs, and AEs leading to discontinuation for patients who received LAMICTAL monotherapy are provided in listings No Final Study Reports are submitted	The Final Study Report is submitted

[a] Studies ongoing on 31 August 1996, which is the data cutoff date for this sNDA

The 27 studies can be grouped as follows:

(1) completed monotherapy studies totaling 868 unique patients and comprised by
  (a) the single *pivotal* trial, US30/31, for approval of the indication of monotherapy: 75 unique LTG patients;
  (b) four *equivalence* trials in initial monotherapy (described as "controlled" and evaluating LTG against either CBZ or PHT: UK49, 89, 74, 106): a total of 446 unique LTG patients;
  (c) one uncontrolled trial (UK105): 1 unique patient;

(2) ongoing monotherapy studies (some uncontrolled, some blinded; not clearly identified in the sponsor's submission); 800 patients were enrolled as of 31 August 1996 (NDA cutoff date), of which 696 represent unique exposures (v 43, p 79);
(3) completed add-on studies in epilepsy (uncontrolled), essentially involving withdrawal to monotherapy; 147/1052 patients were known to have achieved monotherapy;
(4) monotherapy studies conducted by local operating companies (UK, Pakistan, Holland); as of 31 August 1996 (NDA cutoff date), 1060 patients have been enrolled, but "it is unknown how many of these patients achieved monotherapy" (v 43, p 80);
(5) monotherapy trial in migraine (UK78): 37 unique exposures.

Again, the pivotal trial which the sponsor has submitted is US30/31. In April 1994 Glaxo-Wellcome initiated two identical, double-blind, active-control, parallel-treatment efficacy studies (protocols US30 and US31) to evaluate Lamictal as monotherapy in adults refractory to at least one anticonvulsant. An active control study design was chosen because of ethical concerns surrounding the use of placebo in the treatment of a life-threatening disorder like epilepsy. Low-dose valproate (VPA) was selected as active control, and a regimen of 1000 mg/day, or about 15 mg/kg for an average individual, was decided upon since it represents the initial dose recommended in VPA packaging. The study design aimed to demonstrate a treatment difference in efficacy between lamotrigine (LTG) and the active control, while according the control group some protection from seizures. In other words, a treatment difference was not intended to demonstrate overall superiority of LTG to VPA, but rather to show the efficacy of LTG monotherapy in the treatment of partial seizures.

Because of slow patient enrollment, the FDA, in discussion with the sponsor on 29 February 1996, agreed to combine both trials and analyze the data as a single study. New enrollment was closed on 13 March 1996. The study was conducted over a two-year period, 7 April 1994-7 August 1996.

II. EFFICACY

TRIAL DESIGN: After screening (to determine whether the patient or caregiver was able to keep a daily seizure calendar and inclusion/exclusion criteria were met), the patient entered an 8-week Baseline Phase, during which baseline data on seizure frequency were obtained. Patients had to have a minimum of four simple partial, complex partial, and/or secondarily generalized seizures per 4-week period.

Patients were then randomized to receive either LTG or VPA during an 8-week Treatment Phase. The first four weeks saw LTG added to half the patients at 100 mg/day, then escalated by 100 mg/day every week to a target dose of 500 mg/day (see Table 1; all tables can be found at the end of this review); the dose, however, could be lowered to as little as 300 mg/day, as dictated by adverse events (AEs). The other patients received VPA 500 mg bid. The next four weeks consisted of the gradual withdrawal of the concomitant phenytoin or carbamazepine in 20% increments. Once monotherapy was achieved, patients were followed for an additional 12 weeks (Monotherapy Phase).

Clinical assessments were scheduled as follows: patients attended the clinic at screen (week 4), randomization day (Day 0), and thereafter at the end of weeks 2, 4, 8, 12, 16, and 20. Seizure counts were recorded at each visit. (See Table 2.)

The primary outcome measure was the proportion of patients in each group (LTG vs VPA) failing monotherapy ("escapers"), as defined by four escape criteria: (1) doubling of the average monthly seizure count compared to Baseline, (2) doubling of the highest consecutive 2-day seizure

frequency compared to Baseline, (3) emergence of a new seizure type more severe than the current seizure type(s), or (4) clinically significant prolongation of generalized tonic-clonic (GTC) seizures compared to Baseline.

At the conclusion of the 12-week Monotherapy Phase, study medication was withdrawn under double-blind conditions, and treatment with the patient's pretrial regimen (concomitant AED) was reintroduced during a 3-week Follow-up Phase. An additional protocol, Protocol 29, provided two more options: (1) patients who completed 12 weeks on monotherapy (Protocol US30/31) could continue to receive the same double-blind medication (again, LTG and corresponding VPA placebo or VPA and corresponding LTG placebo) without interruption, and (2) patients who completed 12 weeks on monotherapy or discontinued for any reason other than for protocol noncompliance, pregnancy, or consent withdrawal could choose to receive open-label LTG for at least 6 months.

Protocols 30 and 31 were amended three times (two amendments on 12 Sep 1995, and one on 24 Sep 1995). Following are changes that affected study design:

(1) the seizure frequency inclusion criterion was changed from a range complex partial seizures/or secondarily generalized seizures per 4-week period to a minimum of four simple partial, complex partial, and/or secondarily generalized seizures per 4-week period with no upper limit.

(2) inclusion criteria were changed, on 28 June 1994, to mandate at least one uncontrolled secondarily generalized seizure during the 12 weeks preceding screening, so as to allow for subgroup analyses; this criterion was subsequently dropped on 20 Sep 1994 (however, "these amendments were not submitted to the FDA until 12 Sep 1995, although they were implemented at the study sites" [v 5, p 126]).

(3) a continuing eligibility criterion was added at the end of the 8-week Baseline mandating that patients experience a minimum of four seizures per 4-week period, as well as that patients have no more than 20 consecutive seizure-free days during Baseline.

(4) sub-group analysis was added for patients with secondarily generalized seizures of the primary and secondary efficacy endpoints.

(5) because of an increased incidence of rash, patients were not allowed to be placed on a combined LTG and VPA regimen during the follow-up period.

(6) dosing guidelines were clarified such that

  (a) patients were maintained on a stable dose of the concomitant AED throughout the 8-week Baseline;

  (b) patients could not have the dose of the concomitant AED adjusted downward by more than 20% during the first four weeks of the Treatment Transition;

  (c) the taper of the concomitant AED was begun on the first day of Week 13.

(7) the NONMEM analysis described in the original protocol was not done.

INCLUSION/EXCLUSION CRITERIA: ages 13 years and above; minimum of four simple partial, complex partial, and/or secondarily generalized seizures per 4-week period with no upper limit; refractory by history, defined by noncontrol by at least one marketed AED; current therapy must be PHT or CBZ monotherapy for at least the prior 12 weeks. Patients who were resistant to VPA treatment or who developed AEs on VPA were excluded. Other inclusion/exclusion criteria were standard.

POPULATION: 169 patients were randomized (76 to LTG and 80 to VPA). Baseline characteristics for the two groups were as follows (adapted from Table 7):

	LTG (n=76*)	VPA (n=80)
Sex		
Male	43 (57%)	48 (60%)
Female	33 (43%)	32 (40%)
Age (yrs)		
Minimum	13	14
Maximum	73	71
Mean	37	36
Median	36	36
Race		
White	52 (68%)	55 (69%)
Black	8 (11%)	11 (14%)
Oriental	1 (1%)	0
Indian	1 (1%)	0
Other	14 (18%)	14 (17%)
Weight (kg)		
Mean	78.3	70.4
Median	77.7	68.2
Age at 1st seizure (yrs)		
Mean	14.5	15.5
Median	12	13
Duration of seizures (yrs)		
Mean	22.4	20.5
Median	22	20
Patients with history of status epilepticus	7 (9%)	7 (9%)
Presenting seizure at baseline		
Type A	31 (41%)	35 (44%)
Type B	64 (84%)	71 (89%)
Type C	38 (50%)	27 (34%)
Baseline seizure frequency (#/4 weeks)		
Mean	27.2	18.7
Median	9	10
Minimum		
Maximum		
Standard deviation	87.5	30.3
AED at screen		
Carbamazepine	48 (63%)	46 (57.5%)
Phenytoin	28 (37%)	34 (42.5%)
Seizure etiology		
Idiopathic	52 (68%)	49 (61%)
Symptomatic	24 (32%)	31 (39%)

No. of past AEDs	LTG (n=75*)	VPA (n=79)
Mean	4.4	4.6
Median	4	4

*One patient, randomized to the LTG group, mistakenly received VPA/placebo and withdrew after week 12 (v 5, p 147). Hence, the true number of actual LTG-treated patients is 75.

The sole inequality in the above table appears to involve the baseline AED at screening: almost twice as many patients were on CBZ as PHT. However, the current labeling contains no information (and the sponsor has not provided any data) about any appreciable differences in the incidence or types of adverse events that might occur as a result of the interaction of LTG with CBZ as opposed to the interaction of LTG with PHT. Additionally, the plasma concentrations of both CBZ and PHT "were not affected by add-on of LTG" (v 43, p 106), in agreement with information found in the current labeling.

WITHDRAWALS: Study protocol criteria for withdrawal included severe or unacceptable adverse events; deterioration in seizure control to cause clinical concern; serious noncompliance; or other serious illnesses (see Table 3).

In the pivotal monotherapy study (US30/31), 76 patients were randomized to LTG and 80 to VPA. In the LTG group, a total of 48 (63%) patients withdrew from treatment: 15 (19.7%) due to AEs, 4 (3.5%) by withdrawing consent, 2 (2.6%) because of protocol violations, 5 (6.6%) due to inadequate response (which did not meet strict escape criteria), and 22 (28.9%) by meeting escape criteria (lack of efficacy). Among VPA subjects, in comparison, a total of 67 (16%) patients withdrew: 1 (1.2%) died (SUDEP), 6 (7.%%) because of AEs, 2 (2.5%) by withdrawing consent, 4 (5%) because of protocol violation, 3 (3.7%) due to inadequate response, and 51 (63.8%) by meeting escape criteria (v 43, p 83):

Withdrawals (post-randomization)	*LTG (n=76)*	*VPA (n=80)*
During Treatment Transition		
Adverse Event	11	4
Deaths	0	1
Meeting Escape Criteria (efficacy)	15	30
Consent Withdrawal	3	0
Protocol Violation	1	2
Inadequate Response	5	2
During Monotherapy		
Adverse Event	4	2
Deaths	0	0
Meeting Escape Criteria	7	21
Consent Withdrawal	1	2
Protocol Violation	1	2
Inadequate Response	0	1
Total withdrawals (all reasons)	48 (63%)	67 (84%)

According to the sponsor, no data was deleted as a result of protocol deviations (see Table 6), which were regarded as "minor" (v 5, p 146). 56 patients violated or deviated from the protocol (see Table 6), 40 with respect to dosing and 11 regarding the time and events schedule (eg, Treatment Transition was 55 rather than 56 days). However, according to the sponsor "each

patient attempted a 4-week AED taper and a full 12 weeks on LTG or VPA monotherapy. Thus the period of time in which efficacy measurements were made remained constant" (v 5, 146).

Four patients were "inappropriately escaped or continued in the study" (v 5, p 146). One LTG patient and two VPA patients were continued in error after meeting escape criteria, and one VPA patient was withdrawn due to meeting escape criteria when they had not actually been met. One patient, with 26 seizure-free days during Baseline, violated the study continuation criteria.

COMPLIANCE: 52 LTG patients and 67 VPA patients missed at least one dose of concomitant AED dosing. "Cross-checking of the patients who met escape criteria with concomitant AED compliance data indicated that non-compliance with prescribed AED dosing was not associated with any patient meeting escape criteria" (v 5, p 147).

Two LTG and one VPA patient took additional medications with anticonvulsant properties (v 5, pp 148-9): (1) patient 31-14-14076 (LTG), was given an unnamed benzodiazepine for increased seizure activity during week 11, but was then discontinued from the study due to lack of efficacy; (2) patient 31-14-14075 (LTG) took doxepin for 2 days during the Baseline period, then continued in the study, finally meeting escape criteria during week 12, and (3) patient 30-04-04029 (VPA) used lorazepam during Baseline for a cluster of seizures, then continued in the study until meeting escape criteria during week 15.

OUTCOME MEASURES:

PRIMARY: The primary efficacy measure was the proportion of patients meeting escape criteria (*ie,* the number of failures in each group, LTG or VPA) during weeks 13-28 (beginning the first day of the concomitant AED taper) compared to patients who finished the monotherapy treatment period (see the study protocol, v 7, pp 948-9). A patient was classified as "completed," therefore, if he finished 12 weeks on monotherapy or met one of the escape criteria after beginning the AED taper. Escape criteria were defined, relative to baseline, as (1) doubling of the monthly seizure count, (2) doubling of the highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (specifically, seizure type that did not occur during the 8-week baseline) that was more severe than the current seizure type(s), or (4) clinically significant prolongation of generalized tonic-clonic seizures.

The sponsor intended to enroll a maximum of 300 patients (150 patients per study) to obtain 100 completers. Sample size was calculated by using a two-tailed chi-square test on proportions. A difference of 50% between the two treatment groups was assumed. The proportion of patients who would complete 12 weeks on monotherapy was assumed to be 0.60 in the LTG group and 0.30 in the VPA group. Forty-two patients per treatment group would give 80% power at the 0.05 significance level.

A total of 156 patients (91 females, 65 males), aged 13-73, were randomized to receive LTG (n=76) or VPA (n=80). There were, by definition, 114 "completed" patients: 28 finished monotherapy treatment and 22 escaped in the LTG group, and 13 finished monotherapy treatment and 51 escaped in the VPA group. Of the 42 withdrawals (26 in the LTG, and 16 in the VPA, group), 21 were due to AEs (15 for LTG, 6 for VPA).

The analysis the sponsor actually conducted was a two-tailed Cochran-Mantel-Haenzel test to assess whether there were statistically significant differences between treatment groups in the proportion of patients meeting escape criteria. Three analyses were performed, two of which were *post hoc* and not specified in the protocol:

--the per protocol analysis included only patients who met escape criteria or completed 12 weeks of monotherapy;

--two *post-hoc* analyses not specified in the protocol:

(a) an intent-to-treat analysis including all patients randomized who took at least one dose of study medication; all dropouts in the LTG and VPA groups were counted as treatment failure (ie, escaped); and

(b) a "worst-case" analysis among all patients randomized who took at least one dose of study medication; LTG dropouts were counted as escapers and VPA dropouts as completers.

Data from all 156 patients were included in the safety, intent-to-treat, and worst-case analyses; data from the 114 completers were included in the per-protocol efficacy analysis.

SECONDARY: The sponsor used the following three assessments as secondary endpoints:

(1) the difference in the time-to-escape patterns between treatment groups was compared in the per-protocol, intent-to-treat, and worst-case analyses using the log-rank test (adjusted for region and center effects);

(2) assessments of Quality of Life (QOL; by patient questionnaire) and Seizure Severity (SS; by the Liverpool Seizure Severity Scale, a 113-item patient questionnaire evaluating his perception of seizure severity) at the end of Baseline (week 8), Treatment Transition (Week 16), and during and at the end of Monotherapy (Weeks 20 and 28); and

(3) the Investigator's Global Evaluation (IGE), a 7-point rating scale by which the investigator compared the status of the patient (AEs, seizure frequency, etc) to the patient's condition during the Baseline Phase at weeks 12, 16, 20, 24, 28, and 30. By means of the Cochran-Mentel-Haenzel chi-square test (adjusted for center effects), change from baseline within treatment and between treatments were analyzed, as was the proportion of patients who improved, remained the same, or deteriorated from baseline scores ("no change," "mild improvement," "moderate improvement," or "marked improvement").

As a comparative analysis, the difference in the time-to-escape patterns between treatment groups was compared using the Mantel rank order statistic. A Wilcoxen Rank Sum Test was used to assess the change from baseline scores for the Quality of Life (QOL) and Seizure Severity (SS) data. Additionally, a two-tailed Cochran-Mantel-Haenzel test was used for the proportion of patients who improved, remained the same, or deteriorated from specified baseline QOL and SS scores.

OTHER ANALYSES: Subgroup analyses of the primary and secondary efficacy endpoints for patients with secondarily generalized seizures were also conducted.

Plasma concentrations of LTG, VPA, CBZ, and PHT were summarized descriptively. Trough-level concentrations for LTG and VPA were determined at the end of weeks 8, 10, 12, 14, and 16, and random samples for weeks 20, 24, and 28. For CBZ and PHT, trough-level concentrations were taken at the end of weeks 0, 4, 8, 10, 12, 14, and 16.

RESULTS: A total of 156 patients were randomized to treatment (intent-to-treat population), 76 to LTG and 80 to VPA. The per-protocol population consisted of 50 in the LTG group, and 64 in the VPA group. The standard intent-to-treat and "worst-case" analyses consisted of all patients randomized to study medication who received at least one dose of study drug (76 LTG, 80 VPA). Data from each of the 36 centers contributing to the study were also combined on a geographical basis into four regions. The sponsor submitted analyses of three efficacy measures in the study report: (1) the proportion of "completed" patients (primary outcome measure), (2) time-to-treatment failure (secondary outcome measure), and (3) IGE (secondary outcome measure). In the per-protocol analysis, treatment failure was synonymous with meeting escape criteria; whereas in the intent-to-treat population, failure was defined as any patient who escaped or dropped out of the study.

By the per-protocol analysis, the proportion of patients completing 12 weeks of LTG monotherapy was more than twice that for VPA monotherapy (v 1, p 104; see also Tables 18):