CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020764 and 020241/S002

MEDICAL REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20-764
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	Glaxo Wellcome, Inc.
Indication	Epilepsy Efficacy review for use in Lennox-Gastaut Syndrome
NDA Classification	
Original Receipt Date	17 September 1996
Clinical Reviewer	Richard M. Tresley, MD
Review Completed	May 13,.1997

INTRODUCTION: Lamictal was approved as adjunctive therapy in the treatment of partial seizures in adults with epilepsy in 1994. The sponsor has submitted a supplemental NDA for two new indications: (1) use in patients with Lennox-Gastaut syndrome (UK 123), and (2) in patients with secondarily generalized seizures (UK 046 and 086). Jim Murray from Glaxo informed Dr. John Feeney (medical reviewer, FDA) on 4/25/97 that a company's internal audit has raised questions about studies UK 046 and 086 in support of its claim for the use of Lamictal in secondarily generalized seizures: the company may be unable to locate some source documents. The present review will therefore cover only the first indication: use in Lennox-Gastaut syndrome. Review of the efficacy for the second indication, namely, use in secondarily generalized seizures, has been suspended in anticipation of further clarification from the company. Dr. John Feeney has already reviewed the safety evaluation for both indications.

Study UK123 was a multicenter (43 centers in Europe, Australia, and the US; 10 additional centers did not enroll any patients), randomized, double-blind, placebo-controlled study, 2/11/94-11/13/95, comparing add-on lamotrigine to placebo for 16 weeks in 169 children and young adults, aged 2-25 ($n_{treated}$=79; $n_{placebo}$=90), with Lennox-Gastaut seizures.

After screening, candidates entered a four-week single-blind placebo baseline period, following which--if qualified--they were stratified by concomitant anticonvulsant and body weight to one of four dosing regimens and randomized in double-blind fashion to either the treatment or placebo arm for 16 weeks. Included in the 16 weeks was an initial six-week dose-escalation phase. Patients completing the study at Week 16 and not continuing treatment had their study drug tapered off over four weeks in a double-blind manner; those wishing to continue, on the other hand, were tapered off study drug and then placed on open-label lamotrigine.

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.

DOSE: During the four-week single-blind period, patients received either one placebo 5-mg tablet (VPA group) or one placebo 25-mg tablet (non-VPA group). For the 16-week double-blind portion, patients were initially entered in a six-week dose escalation period, followed by two weeks on a fixed dose and a further eight weeks during which the fixed dose could be increased if seizures were still occurring. Recommended doses in mg/kg:

Patient group	*Weeks 1-2*	*Weeks 3-4*	*Weeks 5-8*	*Weeks 9-16*
VPA	0.2 mg/kg	0.5 mg/kg	2.0 mg/kg	5.0 mg/kg (200 mg max dose)
Non-VPA	2.0 mg/kg	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg (400 mg max dose)

Maximum daily doses for lamotrigine (depending on body weight) were thus 100 or 200 mg for patients receiving valproate and 300 or 400 mg for those on other anticonvulsants. The medication was provided as chewable/dispersible tablets of 5-, 25-, and 100-mg strengths. Concomitant AEDS were to maintained at a fixed dose for the duration of the study, but could be reduced in the event of unacceptable side effects, including elevated plasma concentrations.

INCLUSION CRITERIA: ages at treatment onset (excluding patients <15 kg on valproate); more than one predominantly generalized seizure type, including drop attacks (atonic, tonic, major myoclonic) and/or tonic/clonic seizures ≥1 year duration; epilepsy onset <11 years of age; seizure frequency manifested by observable seizures occurring at least every alternate day (or similar average frequency); recent EEG with abnormal background, slow-spike-and-wave (<2.5 HZ) pattern, and lacking a predominantly focal or unifocal abnormality (especially in younger children); at least moderate intellectual impairment, clinical impression of intellectual deterioration in patients with previously normal intellectual function, or mild impairment based on developmental assessments or IQ testing; and no changes in AED dosing <1 month before screening.

EXCLUSION CRITERIA: severe known organic disease (eg, renal or hepatic) which would interfere with drug evaluation; known progressive neurodegenerative disorder; treatment with more than 2 AEDs (excluding additional emergency use of supplemental benzodiazepines); previous exposure to Lamictal; use of an investigational drug <3 months before screen; more than two episodes of major tonic-clonic status epilepticus "in any month in any of the past 6 months"; and (from Amendment 7, dated 4/26/95) use of the ketogenic diet <1 month before screen.

POPULATION: 169 patients were randomized (79 to Lamictal and 90 to placebo); see Tables 5.5-5.6. Baseline characteristics for the two groups were as follows (see Table 5.7-5.8):

	Lamictal	**Placebo**
Sex		
Male	54	45
Female	25	45

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Age (yrs)		
Minimum		
Maximum		
Mean	9.6	10.9
Median	8	10
Race		
White	74	84
Black	3	3
Oriental	1	1
Indian	1	1
Other	0	1
Weight (kg)		
Mean	32.5	34.3
Median	26.5	26
Age at 1st seizure (yrs)		
Mean	1.5	1.3
Median	0.7	0.8
Duration of seizures (yrs)		
Mean	8.9	10
Median	7.6	9.6
Patients with history of status	20	24
History of infantile spasms	31	37
History of Surgery	2	2
Callosotomy	1	2
Resection	1	0
Concomitant AEDs		
VPA	54	51
No VPA	25	39
Seizure etiology		
Idiopathic	41	43
Symptomatic	38	47

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WITHDRAWALS: study protocol criteria for withdrawal included severe or unacceptable adverse event; deterioration in seizure control to cause clinical concern; serious noncompliance; and other serious illness. 179 subjects were enrolled and, of these, 169 eventually randomized; of the 10 not randomized, 8 were due to protocol violations (#99735, 99736, 99738, 99551,99681, 99223, 99061, 99123), 1 to failure to return (#90001), and 1 to consent withdrawal (#99281). Finally, of the 169 subjects randomized, 167 were included in the efficacy analysis; one each of the placebo (PBO) and lamotigine (LTG) subjects had either "no efficacy data or unevaluable efficacy data" (see Table 6). Patient compliance is shown in Table 14.

There were a total of 21 dropouts (12.4%), 22 of whom were on placebo and 9 on Lamictal (an asterisk follows the Lamictal study patient number below [*]; case reports were not submitted for patients marked by a dagger [+]). Of the total,

(a) 3 were due to adverse events (#601* [rash, discontinued day 7; also on VPA], 5504* [Stevens-Johnson, discontinued day 29; also on VPA], 1802* [rash, discontinued day 32; also on

VPA];

(b) 7 to adverse events accompanied by deterioration in seizure control: #2009* [tiredness/asthenia, discontinued day 2; also on VPA], 401+ [discontinued day 56; also on VPA], 901+ [discontinued day 85; also on VPA], 1701+ [discontinued day 43], 3507+ [hypotonia and vigilance decreased, discontinued day 2], 3511+ [no information], 4105+ [no information]);

(c) 1 to consent withdrawal (#503 [no information]);

(d) 2 to seizure deterioration (#3803+ [no information], 2206+ [no information]);

(e) 7 to protocol violations (#5101+ [no information], 3902+ [no information], 3902+ [no information], 5602* [no information], 3504* [no information], 608* [no information], 3508* [no information]); and

(f) 1 to failure to return (#5705+ [no information]).

(See v 1.23, pp 176-87; 1.20, pp 216-22; 1.65, pp 40-287; and 1.66, pp 1-312.)

The sponsor does not distinguish between the enrolled but nonrandomized and the randomized dropouts, and no information is provided for the enrolled but nonrandomized subjects. Presumably the difference between, say, a protocol violation of an enrolled but nonrandomized dropout and that of a randomized dropout may be simply a matter of time: the former violated protocol during the screening period, while the latter after the trial began. The sponsor has been asked to provide a more detailed analysis of dropouts.

PRIMARY OUTCOME MEASURE (incorporating Amendment 7, dated 4/26/95; see the study protocol, v 1.22, pp 316, 366-7): *percent change from baseline in the frequency of "major seizures," defined as drop attacks and tonic-clonic seizures.* Tonic-clonic and drop attacks have been defined in accordance with the International Classification of Epileptic Seizures, 1981 (*Epilepsia* 22 [1981]:489-501, cited v 1.21, p 167):

(1) tonic-clonic seizure: "An attack in which a person has an initial phase of stiffening of the body and thereafter rapid, regular jerking movements of the whole of the body. Consciousness/awareness will be lost."

(2) drop attacks (D2, 4, and 6 by the International Classification) can be: "tonic attacks" or "'[d]rops' with body stiffening and falls backwards"; "atonic attacks" or "'[d]rops' with little or no body stiffening, often bending at the knees, and falls sideways or forwards--often with trauma to the unprotected face"; and "myoclonic attacks" or "'[d]rops' which start with a sudden brief jerk or jerks of face and arms" (v 1.21, p 168).

Atypical absence seizures were not included in the category of "major seizures." According to the sponsor, they were irregularly counted in approximately 50% by parents/carers (v 1.20, p 105).

Analysis of the primary efficacy parameter will be performed in an ITT population (ie, all patients randomized to study medication) and in a protocol-specified population (*ie,* all patients randomized to study medication who reasonably adhered to all protocol requirements). Under the assumptions of normal distribution, with standard deviation 50%, two-tailed significance set at 5%, and an 80% power to detect a difference in percent reduction of at least 32%, then 40 completed patients per treatment are required. In order to allow for subgroup analysis, 54 completed patients per treatment are required. If a dropout rate of 10% is anticipated for the baseline period and 25% after randomization, a total of 160 patients should be recruited for the study.

SECONDARY EFFICACY MEASUREMENTS (by Amendment 7, dated 4/26/95):

(1) percent reduction (compared to placebo baseline) in the number of individual seizure types (atonic, tonic, major myoclonic , and tonic-clonic seizures);

(2) percent reduction (compared to placebo baseline) in the number of atypical absence seizures

(3) Quality of Life assessments (see Appendix II)

(4) global evaluations by (a) clinical investigators and (b) parent/caregivers (see Appendix II).

The Quality of Life assessment, to be completed before randomization and again at the end of the double-blind treatment phase, is a questionnaire completed by parents/caregivers and intended to measure parental/caregiver perceptions of seizure severity, injuries resulting from seizures, level of self-care, and aspects of behavioral and cognitive functions.

One global evaluation will be completed at the end of Week 16 (or earlier on patient withdrawal) by the clinical investigator; scored on a 5-point scale, ranging from "marked deterioration" to "marked improvement," it will describe the investigator's impression of the patient's response to study drug in terms of seizure control (based on seizure diary, parent/caregiver's comments regarding minor--ie, absence--seizures and compared to baseline). A second global evaluation will be completed by the parent/caregiver who will score the patient's general health at Week 16, compared to prior to entry into the study.

Analysis of secondary efficacy parameters will be performed only for the protocol-specific population. Average weekly seizure frequency during both the baseline and the treatment periods will be computed for each patient in order to derive the percent change in seizure frequency on Lamictal and placebo compared to baseline. Comparisons between treatment groups with respect to percent change values will be performed using the extended Mantel-Haenszel chi-square test. Standardized midranks will be used as scores in the analysis in order to compensate for the varying number of patients at each center.

RESULTS: The sponsor failed to specify, in the original protocol, all of the statistical methods to be employed in analyzing data from the trial. Furthermore, at least one of the outcome measures analyzed in the study report, namely, the number of seizure days, was not proposed in the protocol. Furthermore, although not stated in the original protocol, the sponsor decided to include in its analyses all subjects who completed 14 or more of the 16 weeks of the trial.

The sponsor states that, "across all centers, 33% of patients on lamotrigine showed at least a 50% reduction in seizure frequency which was significantly more than the...16% of patients...on placebo (p=0.011, Fisher's exact test) during Weeks 1 to 16" (v 1.20, p 103). During the maintenance phase (Weeks 7 to 16), "significantly more patients on lamotrigine (39%) had at least a 50% reduction in seizure frequency compared to placebo (20%) [p=0.014]" (v 1.20, p 103); see Table 5.10 For the intent-to-treat population treated with lamotrigine, the observed median change from baseline in seizure counts for all major seizures, across all centers, was a 32% reduction with lamotrigine, compared to 9% on placebo, during Weeks 1 to 16, which was statistically significant by nonparametric analysis (p=0.013). During maintenance dosing (Weeks 7-16), the mean reduction across all centers was 35% on lamotrigine compared to 15% on placebo, approaching statistical significance by nonparametric analysis (p=0.054). Unadjusted for center, the estimated difference between LTG and PBO was 21% reduction in seizure counts for both analyzed periods (8.2% to 33.8% for Weeks 1-16 and 4.9% to 36.0% for Weeks 7-16, with a 95% confidence interval). An protocol-specified analysis showed similar results; see Table 5.11.

Three patients on lamotrigine were free of all major seizures during the maintenance phase (3/74 or 4%), compared to none on placebo (0/84), a difference which was not found to be statistically significant (p=0.101).

Older patients showed a greater reduction in seizure counts than younger for Weeks 1-16, but the difference between treatment groups, according to the sponsor, was similar to that seen in the overall population. There were too few nonwhites to note any racial difference. With respect to concomitant VPA treatment, there was a similar change in seizure frequency compared to those not on VPA. A previous history of infantile spasms showed no affect on seizure frequency. See Table 5.12.

Analyzing individual seizure types (secondary outcome measure), the sponsor found:

(1) for the category of all drop attacks: "significantly more patients on LTG, for both Weeks 1-16 (37% LTG, 22% PBO, p=0.037) and Weeks 7-16 (42% LTG, 25% PBO, p=0.039), had a

50% or more reduction in seizure counts" (v 1.20, p 28). For the intent-to-treat population, the observed median reduction in seizure counts across all centers was a statistically significant 34% for the LTG group, versus 9% for PBO, during Weeks 1-16 (p=0.018 by nonparametric test), and almost statistically significant 37% for LTG, versus 17% for PBO, during Weeks 7-16 (p=0.062 by nonparametric test). Unadjusted for center, the estimated difference between LTG and PBO was 21% reduction in seizure counts for both analyzed periods (6.2% to 37.0% for Weeks 1-16 and 2.8% to 37.1% for Weeks 7-16, with a 95% confidence interval). An protocol-specified analysis showed similar results; see Table 5.13.

(2) for tonic-clonic seizures: across all centers, a statistically significant proportion of LTG patients demonstrated at least a 50% reduction in seizure counts, compared to PBO, for Weeks 1-16 (LTG 43%, PBO 20%; p=0.007) as well as Weeks 7-16 (LTG 49%, PBO 27%; p=0.014). For the intent-to-treat population, the observed median reduction in seizure counts was 36% for the LTG group, versus a 10% increase for PBO, for Weeks 1-16 (p=0.014 by nonparametic test), and 48% for the LTG group, versus no change, for PBO for Weeks 7-16 (p=0.024, by nonparametric test). Unadjusted for center, the estimated differences between LTG and PBO were 39% (8.2% to 33.8%, with a 95% confidence interval) for Weeks 1-16 and 33% (4.9% to 36.0%) for Weeks 7-16. An protocol-specified analysis showed similar results; see Table 5.14.

(3) atypical absence seizures were counted irregularly approximately half the patients, and a nonparametric analysis of percent change in seizure counts showed no significant difference between LTG and PBO (v 1.20, p 106). See Table 5.15.

Other secondary measures included (a) the global evaluations by clinical investigators and parent/caretaker, and (b) the quality of life questionnaires. Only LOCF, and not protocol-specified, analyses were done on these two secondary outcome measures. As to the global *evaluations:*

(a) clinical investigator assessments: 75% of LTG patients were judged to have improved on drug, 1% to have deteriorated, and 24% to have shown no change, versus 49%, 1%, and 50%, respectively, for PBO patients. The difference between treatment groups was found to be statistically significant (p=0.002) in favor of LTG. See Table 5.17.

(b) parent/caregiver assessments of changes in general health: 73% of LTG patients were deemed to have improved, 4% to have deteriorated, and 23% to have shown no change, versus 50%, 3%, and 47%, respectively, for PBO. The difference between treatment groups was found to be statistically significant (p=0.006). See Table 5.18.

Quality of life questionnaires were completed about 65 (82%) of patients randomized to LTG and 60 (73%) randomized to PBO for each the subscales of seizure severity (14 items), behavior (9 items), and mood (14 items) as baseline and Week 16. No significant differences between treatment groups were found for seizure severity and behavior. However, a statistically significant treatment effect, in favor of LTG, was recorded for improvement in mood (LTG 62% vs PBO 42%, p=0.047). See Table 5.19-5.20.

Finally, seizure days were not represented as one of the outcome measures in the original protocol; however, the sponsor analyzed the average weekly counts--compared to baseline--of the number of days on which at least one major seizure of any type was reported. Statistically significance was demonstrated for the number of seizure-free days for LTG, compared to PBO): 18% of LTG patients showed at least a 50% reduction in seizure days, versus 7% on PBO, for Weeks 1-16 (p=0.005, by nonparametric analysis of percentage change from baseline in the number of seizure days, adjusted for center), and 23% for LTG and 10% for PBO for Weeks 7-16 (p=0.017). Unadjusted by center, the estimated difference in drug effect was 12% reduction in seizure days for both analyzed phases (3.1% to 20.8% for Weeks 1-16 and 2.9% to 22.7% for Weeks 7-16, with a 95% confidence interval). Results of an protocol-specified analysis were similar; see Table 5.16.

Dr. Sue-Jane Wang (Biostatistics) is in the process of completing her statistical review in an attempt to verify the sponsor's results. She reports that her results are in general agreement

with the sponsor's.

CONCLUSION: There appears to be adequate data affirming the effectiveness of Lamictal in the treatment of Lennox-Gastaut syndrome.

RECOMMENDATIONS:

(1) Await the biostatistical review of Dr. Sue-Jane Wang.

/S/

Richard M. Tresley MD
Medical Reviewer

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TABLES

From v 1.47: Tables 5.5, 5.6, 5.7, 5.8, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17, 5.18, 5.19, 5.20.

From v 1.20: Table 14.

APPENDIX

I Clinical investigator's assessment of change in general health

II Quality of Life questionnaire

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Table 5.5. Summary of Patient Populations Evaluated for Efficacy and Safety

	Lamotrigine	Placebo	Total
Number of Patients Randomized	79	90	169
Number of Pts. in Safety Analyses	79	90	169
No efficacy data or unevaluable efficacy data	1[a]	1[b]	2
Number of Pts in Intent-to-Treat Efficacy analysis	78	89	167
<14 weeks of study treatment	5[c]	13[d]	18
<80% compliance during maintenance dosing	2[e]	1[f]	3
Concurrent AED dose increases	0	2[g]	2
Low lamotrigine plasma level	0	1[h]	1
Number of Pts. in Protocol-specified Analysis	71	72	143

[a] Patient number 608

[b] Patient number 5705

[c] Patient numbers 1802, 2009, 3508, 5504, 5602

[d] Patient numbers 401, 503, 601, 901, 1701, 2206, 3507, 3509, 3511, 3803, 3903, 4105, 5101

[e] Patient numbers 802 and 5505

[f] Patient number 3708

[g] Patient numbers 805 and 4003

[h] Patient number 1302

Table 5.6
Summary of Patient Accountability in UK123

	Lamotrigine	Placebo	Total
Number of Pts. Enrolled	79	100	179
Withdrawn During Placebo Baseline	0	10	10
Number of Pts. Randomized	79	90	169
Number of Pts. Discontinued Prematurely[1]			
Parent withdrew consent	7	14	21
Clin sig deterior of sz control	0	1	1
Patient failed to return	0	2	2
Protocol violation	0	1	1
Adverse Event	4	3	7
	3	7	10
Number of Pts. Completing Study	72	76	148
Number of Pts. Continuing LTG After Study Completion	64	65	129

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[1]One Lamotrigine (#2009) and 2 Placebo patients (#'s 3507 and 3511) withdrew due to a combination of clinically significant deterioration of seizure control and adverse event, and 4 placebo patients (#'s 401, 901, 1701, and 4105) due to deterioration of seizure control classed as a AE. These patients are counted once in the table above as withdrawals due to adverse event.

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Table 5.7
Summary of Demographic Data and Present AED Therapy in UK123

		Lamotrigine	Placebo
Number of Pts. Randomized		79	90
Age (years)	N	79	90
	Mean	9.58	10.90
	Median	8.00	10.00
	S.D.	5.21	5.91
	Min		
	Max		
Race	White	74 (94%)	84 (93%)
	Black	3 (4%)	3 (3%)
	Asian (Indian)	1 (1%)	1 (1%)
	Asian (Oriental)	1 (1%)	1 (1%)
	Other	0 (0%)	1 (1%)
Sex	Male	54 (68%)	45 (50%)
	Female	25 (32%)	45 (50%)
Weight (kg)	N	79	90
	Mean	32.48	34.34
	Median	26.50	26.00
	S.D.	18.05	19.67
	Min		
	Max		
Height (cm)	N	76	88
	Mean	131.69	132.84
	Median	127.00	131.40
	S.D.	23.25	23.37
	Min		
	Max		
Concomitant AEDs	VPA	54 (68%)	51 (57%)
	No VPA	25 (32%)	39 (43%)

Table 5.8
Summary of Neurological History Data in UK123

		Lamotrigine	Placebo
Number of Pts. Randomized		79	90
Age at 1st Seizure (years)	N	70	83
	Mean	1.5	1.3
	Median	0.7	0.8
	S.D.	1.7	1.6
	Min		
	Max		
Duration of Seizures (years)	N	70	83
	Mean	8.9	10.0
	Median	7.6	9.6
	S.D.	5.3	6.0
	Min		
	Max		
Seizure Etiology	Cryptogenic	41 (52%)	43 (48%)
	Symptomatic	38 (48%)	47 (52%)
History of Infantile Spasms Syndrome	Yes	31 (39%)	37 (41%)
	No	48 (61%)	52 (58%)
History of Status Epilepticus	Yes	20 (25%)	24 (27%)
	No	56 (71%)	63 (70%)
	Unknown	3 (4%)	2 (2%)
History of Surgery	Yes	2 (3%)	2 (2%)
	No	77 (97%)	87 (97%)
	Unknown	0 (0%)	0 (0%)
Type of Surgery	Callosotomy	1 (1%)	2 (2%)
	Resection	1 (1%)	0 (0%)

Table 5.10. Change in Seizure Frequency by Type (Compared to Baseline) in Study UK123

		No. of Pts Evaluated	Reduction		No Change	Increase	
			26%–49%	≥50%	±25%	26–49%	≥50%
All Major Seizures (Type D2, D4, D5, or D6)							
Weeks 1–16	LTG	78	21 (27%)	26 (33%)	23 (29%)	3 (4%)	5 (6%)
	PBO	89	17 (19%)	14 (16%)	41 (46%)	7 (8%)	10 (11%)
Weeks 7–16	LTG	74	20 (27%)	29 (39%)	15 (20%)	6 (8%)	4 (5%)
	PBO	84	17 (20%)	17 (20%)	34 (40%)	6 (7%)	10 (12%)
All Drop Attacks (Types D2, D4, or D6)							
Weeks 1–16	LTG	75	19 (25%)	28 (37%)	16 (21%)	5 (7%)	7 (9%)
	PBO	88	14 (16%)	19 (22%)	36 (41%)	6 (7%)	13 (15%)
Weeks 7–16	LTG	71	16 (23%)	30 (42%)	13 (18%)	5 (7%)	7 (10%)
	PBO	83	15 (18%)	21 (25%)	31 (37%)	6 (7%)	10 (12%)
Tonic Clonic Seizures (Type D5)							
Weeks 1–16	LTG	60	6 (10%)	26 (43%)	13 (22%)	3 (5%)	12 (20%)
	PBO	64	7 (11%)	13 (20%)	16 (25%)	4 (6%)	24 (38%)
Weeks 7–16	LTG	57	5 (9%)	28 (49%)	13 (23%)	1 (2%)	10 (18%)
	PBO	60	6 (10%)	16 (27%)	18 (30%)	2 (3%)	18 (30%)

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Table 5.11

Results of Nonparametric Analysis of Percent Change from Baseline in Seizure Frequency in UK123
- All Major Seizures -

Patient Population	Treatment Period	Treatment	Weekly Seizure Count: Baseline N	Baseline Median	Treatment N	Treatment Median	Obs. Median % Change in Seizure Count	Between Treatment Comparison: P-Value[1]	Est. Diff. in Drug Effect[2]	95% C.I.[2]
Intent-to-Treat	Weeks 1 - 16	Lamotrigine	78	16.4	78	9.9	31.7	0.013	20.70	(8.2,33.8)
		Placebo	89	13.5	89	14.2	0.8			
	Weeks 7 - 16	Lamotrigine	78	16.4	78	9.3	35.2	0.054	21.20	(4.9,36.0)
		Placebo	89	13.5	89	12.9	14.6			
Protocol Specified	Weeks 1 - 16	Lamotrigine	71	16.0	71	9.8	32.7	0.026	20.70	(6.5,35.2)
		Placebo	72	14.2	72	13.9	8.5			
	Weeks 7 - 16	Lamotrigine	71	16.0	71	9.1	35.4	0.093	19.00	(2.4,36.1)
		Placebo	72	14.2	72	12.6	17.2			

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[1] Results of CMH test, adjusted for center effects.

[2] Hodges Lehman estimator of the median difference in drug effect and 95% C.I. based on the Wilcoxon rank sum test, unadjusted for center effects. Positive values indicate that the percent change from baseline in seizure counts was in favor of Lamotrigine treatment.

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Table 5.12
Percent Change from Baseline in Frequency of All Major Seizures by Sex, Age, Race, VPA/Non-VPA Status and Infantile Spasms in UK123

Variable	Treatment Period	Category	Treatment	Weekly Seizure Count: Baseline N	Baseline Median	Treatment N	Treatment Median	Obs. Median % Change in Seizure Count
Sex	Weeks 1 - 16	Female	Lamotrigine	25	14.8	25	11.1	32.7
			Placebo	44	15.2	44	15.1	6.0
		Male	Lamotrigine	53	16.8	53	9.3	30.7
			Placebo	45	12.9	45	10.3	12.5
	Weeks 7 - 16	Female	Lamotrigine	25	14.8	25	11.1	33.2
			Placebo	44	15.2	44	14.3	8.7
		Male	Lamotrigine	53	16.8	53	9.1	39.6
			Placebo	45	12.9	45	10.3	18.2
Age	Weeks 1 - 16	<= 12 yrs	Lamotrigine	57	18.5	57	13.3	29.4
			Placebo	55	17.0	55	15.3	8.2
		> 12 yrs	Lamotrigine	21	14.5	21	6.6	51.0
			Placebo	34	11.0	34	11.7	13.1
	Weeks 7 - 16	<= 12 yrs	Lamotrigine	57	18.5	57	11.1	35.0
			Placebo	55	17.0	55	13.3	12.0
		> 12 yrs	Lamotrigine	21	14.5	21	5.2	42.2
			Placebo	34	11.0	34	12.1	18.2
Race	Weeks 1 - 16	Non White	Lamotrigine	5	28.5	5	12.1	48.9
			Placebo	6	6.5	6	9.7	-27.9
		White	Lamotrigine	73	16.3	73	9.8	30.7
			Placebo	83	15.5	83	14.4	9.3
	Weeks 7 - 16	Non White	Lamotrigine	5	28.5	5	9.1	60.0
			Placebo	6	6.5	6	13.1	-30.6

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Table 5.12
Percent Change from Baseline in Frequency of All Major Seizures by Sex, Age, Race, VPA/Non-VPA Status and Infantile Spasms in UK123

Variable	Treatment Period	Category	Treatment	Weekly Seizure Count: Baseline N	Baseline Median	Treatment N	Treatment Median	Obs. Median % Change in Seizure Count
Race	Weeks 7 - 16	White	Lamotrigine	73	16.3	73	9.4	35.0
			Placebo	83	15.5	83	12.9	16.9
VPA	Weeks 1 - 16	Non VPA	Lamotrigine	25	16.8	25	9.9	34.0
			Placebo	39	20.8	39	18.4	13.7
		VPA	Lamotrigine	53	16.3	53	9.8	30.7
			Placebo	50	10.8	50	9.8	5.4
	Weeks 7 - 16	Non VPA	Lamotrigine	25	16.8	25	9.2	37.2
			Placebo	39	20.8	39	18.1	17.9
		VPA	Lamotrigine	53	16.3	53	9.9	35.0
			Placebo	50	10.8	50	8.6	5.9
Infantile Spasm	Weeks 1 - 16	Infantile Spasms	Lamotrigine	30	13.6	30	9.8	34.5
			Placebo	37	17.0	37	22.3	8.2
		No Infantile Spasms	Lamotrigine	48	20.3	48	11.1	29.8
			Placebo	51	12.9	51	10.6	9.3
	Weeks 7 - 16	Infantile Spasms	Lamotrigine	30	13.6	30	9.7	35.2
			Placebo	37	17.0	37	18.7	12.0
		No Infantile Spasms	Lamotrigine	48	20.3	48	8.9	37.3
			Placebo	51	12.9	51	10.2	18.8

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Table 5.13
Results of Nonparametric Analysis of Percent Change from Baseline in Seizure Frequency in UK123
- All Drop Attacks -

Patient Population	Treatment Period	Treatment	Weekly Seizure Count				Obs. Median % Change in Seizure Count	Between Treatment Comparison		
			Baseline		Treatment			P-Value[1]	Est. Diff. in Drug Effect[2]	95% C.I.[2]
			N	Median	N	Median				
Intent-to-Treat	Weeks 1 - 16	Lamotrigine	75	14.5	75	7.1	33.8	0.018	21.20	(6.2,37.0)
		Placebo	88	11.6	88	10.5	8.9			
	Weeks 7 - 16	Lamotrigine	75	14.5	75	6.5	37.2	0.062	21.40	(2.8,37.1)
		Placebo	88	11.6	88	10.4	17.4			
Protocol Specified	Weeks 1 - 16	Lamotrigine	69	14.0	69	7.1	33.8	0.023	21.90	(5.6,39.4)
		Placebo	72	11.6	72	10.5	8.5			
	Weeks 7 - 16	Lamotrigine	69	14.0	69	5.8	37.2	0.060	21.40	(1.8,38.4)
		Placebo	72	11.6	72	9.6	16.7			

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[1] Results of CMH test, adjusted for center effects.

[2] Hodges Lehman estimator of the median difference in drug effect and 95% C.I. based on the Wilcoxon rank sum test, unadjusted for center effects. Positive values indicate that the percent change from baseline in seizure counts was in favor of Lamotrigine treatment.

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Table 5.14

Results of Nonparametric Analysis of Percent Change from Baseline in Seizure Frequency in UK123
- Tonic-Clonic Seizures -

Patient Population	Treatment Period	Treatment	Weekly Seizure Count: Baseline N	Baseline Median	Treatment N	Treatment Median	Obs. Median % Change in Seizure Count	Between Treatment Comparison: P-Value[1]	Est. Diff. in Drug Effect[2]	95% C.I.[2]
Intent-to-Treat	Weeks 1 - 16	Lamotrigine	60	2.7	60	1.4	35.8	0.014	38.65	(1.6,67.8)
		Placebo	64	1.0	64	1.2	-9.8			
	Weeks 7 - 16	Lamotrigine	60	2.7	60	1.2	48.4	0.024	33.30	(0.0,67.2)
		Placebo	64	1.0	64	1.1	0.0			
Protocol Specified	Weeks 1 - 16	Lamotrigine	55	2.8	55	1.3	35.7	0.101	30.00	(0.0,60.3)
		Placebo	51	1.0	51	1.1	-8.5			
	Weeks 7 - 16	Lamotrigine	55	2.8	55	1.1	48.4	0.127	20.30	(0.0,56.7)
		Placebo	51	1.0	51	0.9	0.9			

[1] Results of CMH test, adjusted for center effects.

[2] Hodges Lehman estimator of the median difference in drug effect and 95% C.I. based on the Wilcoxon rank sum test, unadjusted for center effects. Positive values indicate that the percent change from baseline in seizure counts was in favor of Lamotrigine treatment.

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Table 5.15 q6b5(n01efs09) 20AUG96 13:48

Results of Nonparametric Analysis of Percent Change[1] from Baseline in Atypical Absence Seizures in UK123

		Seizure Count					
		Baseline		Treatment			
Patient Population	Treatment	N	Median	N	Median	Obs. Median % Change in Seizure Count	P-Value[2]
Intent-to-Treat	Lamotrigine	47	2.0	47	1.0	13.3	0.744
	Placebo	44	2.0	44	1.1	37.8	
Protocol Specified	Lamotrigine	44	2.0	44	1.0	11.7	0.942
	Placebo	38	1.0	38	1.1	37.8	

[1]Percent Change is based on ((seizure count at baseline - average of seizure count at study phase week 2, 4, 8, 12 and 16) / seizure count at baseline) * 100. Percent change is set to -100 if seizure count at baseline is 0 and average seizure counts is greater than 0. Positive value means reduction of seizure from baseline.

[2]Cochran-Mantel Haenszel (CMH) test, adjusted for center effect.

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Table 5.16

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Results of Nonparametric Analysis of Percent Change from Baseline in Total Seizure Days in UK123

Patient Population	Treatment Period	Treatment	Weekly Seizure Day				Obs. Median % Change in Seizure Day	Between Treatment Comparison		
			Baseline		Treatment			P-Value[1]	Est. Diff. in Drug Effect[2]	95% C.I.[2]
			N	Median	N	Median				
Intent-to-Treat	Weeks 1 - 16	Lamotrigine	78	6.0	78	4.2	17.3	0.005	11.70	(3.10,20.80)
		Placebo	89	5.8	89	5.1	2.9			
	Weeks 7 - 16	Lamotrigine	78	6.0	74	3.8	21.8	0.017	11.70	(2.90,22.70)
		Placebo	89	5.8	84	4.7	3.3			
Protocol Specified	Weeks 1 - 16	Lamotrigine	71	6.0	71	4.4	16.0	0.048	9.40	(1.40,20.00)
		Placebo	72	5.8	72	5.1	3.7			
	Weeks 7 - 16	Lamotrigine	71	6.0	71	3.8	15.4	0.109	8.90	(0.00,20.60)
		Placebo	72	5.8	72	4.6	3.8			

[1] Results of CMH test, adjusted for center effects.

[2] Hodges Lehman estimator of the median difference in drug effect and 95% C.I. based on the Wilcoxon rank sum test, unadjusted for center effects. Positive values indicate that the percent change from baseline in seizure days was in favor of Lamotrigine treatment.

Table 5.17 q6b5(n01efs04) 20AUG96 13:52

Summary of Investigator's Global Evaluation of Seizure Control at Week 16 in UK123
Protocol-Specified Population

Treatment Group	N	Improvement[1]			No Change[1]	Deterioration[1]		P-Value[2]
		Total	Marked	Some		Some	Marked	
Lamotrigine	71	53 (75%)	18 (25%)	35 (49%)	17 (24%)	0 (0%)	1 (1%)	0.002
Placebo	72	35 (49%)	9 (13%)	26 (36%)	36 (50%)	1 (1%)	0 (0%)	

[1] Entries are the number and percent of patients with the specified response.

[2] P-Value is derived from Fisher's exact test to compare Lamotrigine and Placebo with respect to the proportion of patients with improvement in seizure control.

Table 5.18
Summary of Parent/Carer's Evaluation of General Health at Week 16 in UK123

Treatment Group	N	Improvement[1]			No Change[1]	Deterioration[1]		P-Value[2]
		Total	Marked	Some		Some	Marked	
Lamotrigine	71	52 (73%)	21 (30%)	31 (44%)	16 (23%)	1 (1%)	2 (3%)	0.006
Placebo	72	36 (50%)	9 (13%)	27 (38%)	34 (47%)	2 (3%)	0 (0%)	

[1] Entries are the number and percent of patients with the specified response.

[2] P-Value is derived from Fisher's exact test to compare Lamotrigine and Placebo with respect to the proportion of patients with improvement in seizure control.

Table 5.19. Quality of Life Total Score Scales
Number of patients improved, deteriorated or showing no change

		N	Improved	No Change	Deteriorated	Fisher's Exact Test P-value
1. Severity	LTG	56	36 (64%)	3 (5%)	17 (30%)	0.646
	PBO	64	38 (59%)	2 (3%)	24 (38%)	
2. Behaviour	LTG	65	36 (55%)	8 (12%)	21 (32%)	0.912
	PBO	66	35 (53%)	10 (15%)	21 (32%)	
3. Patient Mood	LTG	65	40 (62%)	8 (12%)	17 (26%)	0.047
	PBO	64	27 (42%)	7 (11%)	30 (47%)	

Table 5.20
Between Treatment Comparison of Quality of Life in UK123
Total Scores - Seizure Severity, Behaviour and Mood

	Lamotrigine (N= 79)		Placebo (N= 90)		Treatment Comparison	
Total Score Scales	N	Median % Change from Baseline	N	Median % Change from Baseline	Est. of Median Diff.	95% C.I. [1]
Severity	56	10.6	64	7.1	5.2	(-3.40,14.10)
Behaviour	65	4.8	66	4.3	1.0	(-4.50,8.00)
Patient Mood	65	6.9	64	0.0	7.9	(2.80,14.10)

[1] Hodges Lehman estimator of the median difference in drug effect and 95% C.I. based on the Wilcoxon rank sum test, unadjusted for center effects.

Table 14. Summary of Estimated Patient Compliance

Project 105-123
(Data as of: February 26, 1996)

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Table 14
Summary of Estimated Patient Compliance

Compliance Category		Lamotrigine (N= 79)	Placebo (N= 90)
Excess	(> 100%)	29 (37%)	38 (42%)
Excellent	(100%)	2 (3%)	6 (7%)
Good	(80 - 99%)	44 (56%)	44 (49%)
Poor	(50 - 79%)	4 (5%)	2 (2%)

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LAMOTRIGINE TRIAL

94

H34-046-C-86

PATIENT INITIALS	PATIENT NUMBER	WEEK	DATE
		28	D / M / Y

INVESTIGATOR GLOBAL EVALUATION

INSTRUCTIONS: Based on your knowledge of this patient and according to relevant factors (e.g., adverse experiences, seizure intensity, duration, frequency, etc.), compare his status during this treatment to the pretreatment period. Enter the appropriate number on the line next to the item. (Only one response)

1 = Marked Deterioration
2 = Moderate Deterioration
3 = Mild Deterioration
4 = No Change
5 = Mild Improvement
6 = Moderate Improvement
7 = Marked Improvement

_____

INVESTIGATOR COMMENT LOG

Date (D/M/Y)	

APPENDIX A10

SEIZURE SEVERITY, MOOD AND QUALITY OF LIFE QUESTIONNAIRE

CONFIDENTIAL

Serial
Number

Please read the notes below before filling in the questionnaire.

i) Most of the questions can be answered by ticking the appropriate box next to the answer that applies to you. Sometimes you are asked to answer in your own words; please use the space provided.

ii) Usually after answering a question you go on to the next one, unless your answer means that some subsequent questions do not apply to you. In that case, please find the enclosed instructions which will direct you to the next appropriate question.

Although the questionnaire may look rather long, you will find that it is not necessary for you to answer all the questions. By following the instructions carefully, you will miss out some questions which do not apply to you.

iii) If you are unable to answer a question for some reason please write this on the questionnaire.