

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

PHARMACOLOGY REVIEW(S)

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 24, 1997

FROM: Glenna G. Fitzgerald, Ph.D. /S/
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-764
Lamictal CD tablets
Sponsor: GlaxoWellcome

SUBJECT: Approvability

**APPEARS THIS WAY
ON ORIGINAL**

There were no preclinical studies submitted to this NDA for a new formulation for Lamictal and there are no unusual excipients in the new formulation. The pharmacology and toxicology studies submitted to NDA 20-241 for Lamictal tablets support approval of the CD dosage form and no additional studies are needed.

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APPLICATION NUMBER: 020764 and 020241/S002

STATISTICAL REVIEW(S)

JUN 27 1997

STATISTICAL REVIEW AND EVALUATION

DET/IRM

JUN 27 1997

NDA#: 20-764

Applicant: Glaxo-Wellcome, Inc.

Name of Drug: Lamictal CD tablets (lamotrigine)

Indication: I. Adjunctive treatment of Lennox-Gastaut Syndrome in pediatric and adult patients (UK123)
II. Adjunctive treatment of secondarily generalized tonic-clonic seizures in adults (UK46 and UK86).

Documents Reviewed: Vols. 1.1, 1.20,22,24,28,47,51,53,55,56 Dated Sept. 23, 1996
SAS Database, received Sept 24, 1996 for UK123
SAS Database, received Nov. 20, 1996 for UK46 and UK86

Medical Officers: Richard Tresley, M.D., John Feeney, M.D. (HFD-120)

The medical division received a fax (to be followed by an official submission) from the sponsor on May 14, 1997. The fax was a copy of the sponsor's letter formally withdrawing studies UK46 and UK86 from this NDA submission. After consultation with Dr. Chi, Director, Division of Biometrics, it was decided that the statistical review of this NDA should exclude these two trials.

The following review has been discussed with the medical reviewers and team leader. The tables/figures from the sponsor are labeled as Table/Figure xS and those from this reviewer's evaluation and analyses are labeled as Table xR or Figure xR.

1 BACKGROUND

In mid September, 1996, Glaxo-Wellcome Inc. submitted lamotrigine (Trade name: Lamictal CD tablets) NDA in support of indications as adjunctive treatment for both pediatric and adult patients with a clinical diagnosis of a Lennox-Gastaut Syndrome (severe generalized epilepsies of childhood onset) [indication-1] and as adjunctive treatment for adult patients with secondarily generalized tonic-clonic seizures [indication-2]. Eleven clinical studies were submitted for indication-1, including one controlled trial (UK123), four ongoing trials and six uncontrolled trials. All 11 trials were evaluated for safety. In addition, two double-blind, placebo-controlled, two-treatment, two-period crossover trials (UK46 and UK86) were submitted for indication-2.

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Lamictal Tablets, a compressed tablet formulation of lamotrigine, was approved on December 27, 1994 (see NDA 20-241). The sponsor noted that it has been marketed in the United States since February 1995 for adjunctive therapy of partial seizures in adults with epilepsy.

2 PIVOTAL TRIALS

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2.1 TRIAL UK123

Protocol - "Lamotrigine as Add-on therapy in patients with a clinical diagnosis of a Lennox-Gastaut Syndrome (severe generalized epilepsy of childhood onset). A multicenter, Double-Blind, Placebo Controlled, Parallel Group study"

2.1.1 STUDY DESCRIPTION

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TRIAL DESIGN

UK123 is a randomized, double-blind, placebo-controlled, international multicenter (43 centers in 12 countries) clinical trial. All patients received one placebo 5 mg tablet (VPA groups) or one placebo 25 mg tablet (non-VPA groups) daily during the single-blind 4-week placebo baseline period for entry eligibility confirmation. Eligible patients were (see Appendix I, inclusion/exclusion criteria at screen) stratified according to their concomitant standard antiepileptic drugs (AEDs) and body weight to the appropriate dosing regimen and randomized to receive either lamotrigine (LTG) or placebo (PBO) for 16 weeks with clinic visits at regular intervals. Randomization codes were computer generated and assigned to patients by selecting the double-blind medication pack corresponding to the next available consecutive number of the appropriate dose schedule at the end of the placebo baseline phase. Lamotrigine was provided in the form of white, black currant flavored, chewable/dispersible tablets of 5, 25 and 100 mg strengths. Placebo tablets were identical in appearance, color and taste. Dose escalation took place over the first 6 weeks of the treatment period, followed by a fixed dose period of 2 weeks. The remaining 8 weeks is the dose maintenance period. However, the dose can either remain the same or be increased further at this stage, if the patient is still experiencing seizures. At each visit, the seizure counts, seizure types, adverse experiences (AE), and quality of life assessments (QOL) were recorded. Criteria for early withdrawal of the trial were development of unacceptable AE, patients failed to return, withdrew consent, protocol violation, general condition deteriorated, and clinically significant deterioration of seizure control.

TRIAL OBJECTIVE

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The aim of the study was to establish efficacy as add-on therapy for 16 weeks in treating patients with a clinical diagnosis of a Lennox-Gastaut Syndrome. The efficacy measurements were per protocol:

- % reduction (compared to placebo baseline) in total seizures (drop attacks, tonic-clonic seizures and atypical absence seizures).
- % reduction (compared to placebo baseline) in number of individual seizure types - atonic, tonic, major myoclonic and tonic-clonic seizures.
- % reduction (compared to placebo baseline) in number of atypical absence seizures
- QOL assessments
- Global evaluations

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All drop attacks and tonic-clonic seizures occurring each day following the screen visit were recorded by the parent/carer on a seizure diary. Seizure counts were transcribed into the CRF by the investigator or delegated representative at each clinic visit. Seizures were classified according to the International Classification of Seizures (1981) (Appendix II), and parents/carers were given appropriate descriptions of each seizure type to help with recognition. When present, atypical absence seizures were counted for one hour before (by parent/carer) or during (by investigator) each clinic visit after screen. Whenever possible, the counting was carried out by the same person for each individual patient throughout the study. The time of day of these counting periods was fixed and adhered to throughout.

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Investigator global evaluation was a 5 point scale ranging from "marked deterioration" to "marked improvement" for the patient's response to study medication in terms of seizure control at the end of the double-blind phase or earlier on patient withdrawal, relative to seizure control prior to entry to the study.

The primary outcome measure (stated in the power calculation of the data handling and analysis section) was the percentage reduction in drop attacks/tonic-clonic seizures, comparing the study period to the baseline period. The evaluation of safety is based on patients reports of adverse experiences, haematology, biochemistry screening, physical and neurological examinations and vital signs.

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STATISTICAL PLAN

The statistical analysis/efficacy measurements (Appendix x, vol.1.22, p.316) section of the protocol stated that "these variables will be summarized by treatment using tables and/or graphs as appropriate, and formal tests of significance will be used to compare all efficacy measures. Confidence intervals will be derived for relevant parameters associated with these tests". There was no statistical analysis plan explicitly described in the original protocol (Protocol submission Sep. 1993). The trial started in February 1994 and was completed in November 1995. Protocol amendment #7 (April 26, 1995), applied to efficacy analyses (to be commented in sec. 2.1.3 REVIEWER'S EVALUATION AND COMMENTS), was 1) The primary outcome measure in this trial will be percentage change from baseline in frequency of major seizures (drop attacks and tonic-clonic seizures); 2) Atypical absence seizures will not be pooled with drop attacks and tonic-clonic seizures in order to derive a total count of major seizures; 3) The secondary outcome measures in this trial will be % reduction in number of

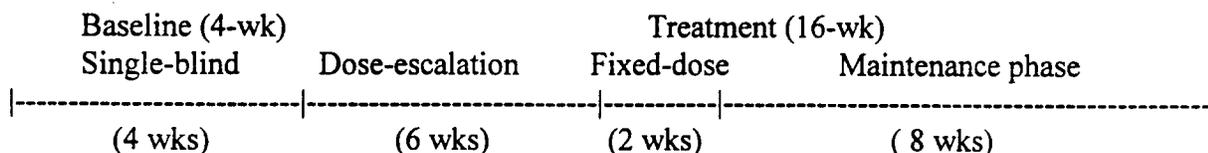
individual seizure types, % reduction in number of atypical absence seizures, QOL assessments, and Global evaluations; 4) Analysis of the primary efficacy parameter will be performed in an intent-to-treat population (defined as all patients randomized to study medication) and in a protocol-specified population (defined as all patients randomized to study medication who reasonably adhered to all protocol requirements). Analysis of the secondary efficacy parameters will be performed only in the protocol-specified 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 lamotrigine (LTG) and placebo (PBO) treatment compared to baseline. Comparisons between treatment groups with respect to percent change values will be performed using the extended Mantel-Haenszel chi-square test [stratified by center]. Standardized midranks will be used as scores in the analysis in order to standardize for the varying number of patients at each center.

Sample size estimation was based on the % reduction in drop attacks/tonic-clonic seizures. A total of 160 patients (80 patients per arm) were derived to detect a minimum of 32% reduction of seizure counts from baseline with 80% power, assuming % reduction is approximately normally distributed, with standard deviation 50%, 25% increase of patients for any subgroup analysis, 10% dropout at the baseline period, 25% dropout at the treatment period, using 2-sided test at the 5% significance level.

2.1.2 OVERVIEW OF THE RESULTS (UK123)

Time Line of the Trial

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One hundred and seventy-nine patients, _____ years of age, entered into the study. Of those ten patients were not randomized (1-fail to return, 1-withdrew consent, 7-protocol violation). These patients were recruited from 43 centers in 12 countries. For efficacy analysis, the protocol specified analysis consists of 80% and 90% of the randomized patients in placebo and lamotrigine arms, respectively.

The percentage of premature discontinuations from the study were 9% in the Lamital treated group and 16% in the placebo treated group (see Table 1S). The reasons for discontinuation were mostly adverse events (6%) and protocol violation (4%).

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Table 1S. Summary of patients' accountability (Tables 5.5, 5.6 of vol. 47) - UK123

	Lamotrigine	Placebo	Total
Number of patients enrolled	79	100	179
Number of patients randomized	79	90	169*
# of patients discontinued prematurely	7 (9%)	14 (16%)	21 (12%)
Patient withdrew consent	0	1 (1%)	1 (.6%)
Clinical sig. Deterioration of seizure control	0	2 (2%)	2 (1%)
Patient failed to return	0	1 (1%)	1 (.6%)
Protocol violation	4 (5%)	3 (3%)	7 (4%)
Adverse Event	3 (4%)	7 (8%)	10 (6%)
Number of pts completing study	72 (91%)	76 (84%)	148(88%)
Number of pts continuing LTG after study completion	64	65	129
# of pts in safety analysis	79	90	169
no or unevaluable efficacy data	1	1	2
# of pts in ITT efficacy analysis	78	89	167
<14 wks of study treatment	5	13	18
<80% compliance during maintenance	2	1	3
Concurrent AED dose increases	0	2	2
Low lamotrigine plasma level	0	1	1
# of pts. in protocol-specified analysis	71 (90%)	72 (80%)	143

* 10 patients who withdrew during placebo baseline were not randomized.

There were more males (68% vs. 32%) in the lamotrigine arm and equal numbers of males:females in the placebo arm. Patients in the lamotrigine arm had a lower median age (8yrs vs. 10yrs). More than 90% of the patients were White. Sixty-eight percent (68%) of lamotrigine patients received VPA as part of their AED treatment regimen compared to 57% of placebo patients. The neurological history including age at first seizure, duration of seizures, seizure etiology (50% cryptogenic and 50% symptomatic), and history of infantile spasms, status epilepticus were similar between the two treatment arms.

Primary efficacy endpoint - Seizure frequency of all major seizures

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All major seizures include all drop attacks (Appendix II, Types D2, D4 or D6) and tonic-clonic seizures (Type D5). Table 2S summarizes the results for seizure frequency (intent-to-treat population) for treatment phase (weeks 1-16) and maintenance phase (weeks 7-16), separately. For weeks 1-16, more patients (33%) in the lamotrigine treated group showed a $\geq 50\%$ reduction in seizure frequency than those (16%) in the placebo treated group ($p=.011$). The rates were 39% for the lamotrigine group and 20% for the placebo group during the maintenance phase ($p=.014$).

A nonparametric analysis of percent change from baseline in the frequency of all major seizures adjusted for center (Cochran-Mantel-Haenszel test, CMH) indicated a significantly greater median reduction from baseline in the frequency of all major seizures for lamotrigine compared to placebo for weeks 1-16 (32% vs. 9%, $p=.013$) and for weeks 7-16 (35% vs. 15%, $p=.054$). The estimated difference between lamotrigine and placebo unadjusted for center was a 21% reduction in seizure counts for both analyzed phases (95% CI=8.2% to 33.8% for weeks 1-16 and 4.9% to 36.0% for weeks 7-16).

Required subgroup analyses can be found in Appendix III (Table 5.12 of vol.1.47). For gender, a subset analysis showed that median percent change in seizure count was similar in both male and female patients. Patients on lamotrigine consistently showed a greater reduction in seizure frequency than did patients on placebo for both genders. For age, older patients had a greater reduction in seizure frequency (51%) on lamotrigine compared with the younger group (29%) for weeks 1-16. This difference was not as large (42% for > 12-yr vs. 35% for \leq 12-yr) in the weeks 7-16 analysis. The placebo percentage reduction was also higher in older children compared to younger children during both the weeks 1-16 and weeks 7-16 analyses. For race, more than 90% of the patients were White; the subgroup analysis was non-conclusive.

For the analysis of the CMH test adjusted for centers and nonparametric analysis of the % change from baseline, please see sec. 2.1.3 REVIEWER'S EVALUATION AND COMMENTS.

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Table 2S. Change in seizure frequency by type compared to baseline - UK123 (Tables 5.10,5.11,5.13,5.14 of vol.47)

ITT	≥50% reduction from baseline		p-value (WRS)	median % change in sz count		p-value* (CMH)	Est. Diff** (LTG-PBO)	95% CI *** in %
	Lamotrigine	Placebo		Lamotrigine	Placebo			
All major types Wk1-16 Wk7-16	33%(26/78)	16%(14/89)	.011	32%	9%	.013!	20.70%	8.2%, 33.8%
	39%(29/74)	20%(17/84)	.014	35%	15%	.054	21.20%	4.9%, 36.0%
All drop attacks Wk1-16 Wk7-16	37%(28/75)	22%(19/88)	.037	34%	9%	.018	21.20%	6.2%, 37.0%
	42%(30/71)	25%(21/83)	.039	37%	17%	.062	21.40%	2.8%, 37.1%
Tonic-Clonic sz Wk1-16 Wk7-16	43%(26/60)	20%(13/64)	.007	36%	-10%	.014	38.65%	1.6%, 67.8%
	49%(28/57)	27%(16/60)	.014	48%	0%	.024	33.30%	0.0%, 67.2%

* results of CMH test, adjusted for center effects

** Hodges Lehman estimator of the median difference in drug effect

*** 95% CI based on the Wilcoxon rank sum test, unadjusted

! please see section 2.1.3 REVIEWER'S EVALUATION AND COMMENTS

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Secondary efficacy endpoints

- All drop attacks (atonic, tonic, myoclonic seizures) - Types 2, 4 or 6

Both weeks 1-16 and weeks 7-16 analyses showed that more patients had $\geq 50\%$ reduction in drop attacks in the lamotrigine treated group than in the placebo treated group (wk1-16: 37% vs. 22%, $p=.037$; wk7-16: 42% vs. 25%, $p=.039$). A significantly greater reduction from baseline in the frequency of all drop attacks was observed in the lamotrigine arm when compared to the placebo arm (34% vs. 9%, $p=.018$ for wk1-16; 37% vs. 17%, $p=.062$ for wk7-16). The estimated difference between lamotrigine and placebo unadjusted for center was a 21% reduction in seizure counts for both analyzed periods (95% CI: 6.2% to 37.0% for wk1-16 and 2.8% to 37.1% for wk7-16). These results can be found in the second part of Table 2S.

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- Tonic-Clonic seizures - Type 5

Both weeks 1-16 and weeks 7-16 analyses showed that more patients had $\geq 50\%$ reduction in tonic-clonic seizures in the lamotrigine treated group than in the placebo treated group (wk1-16: 43% vs. 20%, $p=.007$; wk7-16: 49% vs. 27%, $p=.014$). A significantly greater reduction from baseline in the frequency of tonic-clonic seizures was observed in the lamotrigine arm when compared to the placebo arm (36% vs. 10%, $p=.014$ for wk1-16; 48% vs. 0%, $p=.024$ for wk7-16). The estimated difference between lamotrigine and placebo unadjusted for center was a 39% reduction in seizure counts for weeks 1-16 (95% CI: 1.6% to 67.8%) and a 33% reduction in seizure counts for weeks 7-16 (95% CI: 0% to 67.2%). Third part of Table 2S summarizes these results.

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- Atypical absence seizures

Atypical absence seizures were counted irregularly for approximately 50% of patients by parents/carers in most cases. Analysis of percentage change in counts of atypical seizures from baseline (CMH test adjusted for center) showed no significant differences between lamotrigine and placebo.

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- Seizure days

Please see sec. 2.1.3. REVIEWER'S EVALUATION AND COMMENTS.

- QOL assessments

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Quality of life total score scales for seizure severity, behavior, and patient mood were summarized. Except for patient mood (62% improved in lamotrigine group and 42% improved in placebo group, $p=.047$), there were no difference between treatments in behavior scores ($p=.912$, Fisher's Exact test) or seizure severity ($p=.646$, Fisher's Exact test). Please see reviewer's Evaluation and Comments for intent-to-treat evaluation.

- Global evaluations

At the end of the double-blind phase or earlier on patient withdrawal, both investigator and parent/carer evaluations were performed. There were significantly more patients in the lamotrigine group (75%: 53/71) than in the placebo group (49%: 35/72) were assessed by the investigator as having marked or some improvement ($p=.002$). These percentages were 73% (52/71) in the lamotrigine group and 53% (36/72) in the placebo group when evaluated by parent/carer ($p=.006$). Please see sec. 2.1.3 REVIEWER'S EVALUATION AND COMMENTS for intent-to-treat evaluation.

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2.1.3 Reviewer's Evaluation and Comments

The ITT analysis defined by the sponsor consisted of 78 patients for lamotrigine treated group and 89 patients for placebo treated group (see Table 1S). The electronic database submitted contains 78 patients for lamotrigine arm and 90 for placebo arm.

The primary efficacy analysis prespecified in the amendment #7 was the median % change in all major seizure count using the extended Mantel-Haenszel chi-square test with standardized midrank scores adjusted for centers. In addition, a supplemental analysis was performed on the primary efficacy variable adjusted for countries (pooled centers). The adjustment was performed by checking the poolability of the data via visual inspection, the data were pooled by country and Somer's index; homogeneity was tested by considering four major centers: three largest countries (France, Spain and the US) and all other remaining centers combined.

This reviewer summarizes the distribution of patients by center and by country (Table 1R). The sample size of a given center ranged from no patient to at most 9 patients. There were 10 centers with patient(s) only assigned to one treatment. Randomization within each center seemed reasonable with possible exceptions for Centers 4, 6, 41 from France and Center 51 from US. Centers 4 and 6 each had two patients and both patients were assigned to the placebo arm. Center 41 had more patients in the placebo arm ($n=5$) than in the lamotrigine arm ($n=3$). Center 51 had all three patients assigned to placebo arm. The sample ratio of lamotrigine vs. Placebo were 25:34 for France, 13:12 for Spain, 13:16 for US; and 27:28 for other countries combined.

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Table 1R. Distribution of patients by center - UK123

OBS	Center	lamotrigine	placebo	country
1	.	1	.	.
2	4	.	2	F
3	5	3	3	O
4	6	.	2	F
5	7	3	3	F
6	8	3	2	F
7	9	1	1	O
8	11	1	2	O
9	12	2	2	O
10	13	1	1	O
11	14	2	2	O
12	16	.	1	O
13	17	.	1	O
14	18	2	2	O
15	20	4	5	O
16	21	3	2	S
17	22	3	3	S
18	23	4	3	S
19	24	3	4	S
20	27	3	2	O
21	29	1	.	O
22	32	1	.	O
23	34	3	2	O
24	35	3	3	F
25	37	.	1	F
26	38	3	4	F
27	39	2	3	F
28	40	1	2	F
29	41	3	5	F
30	42	1	2	F
31	43	2	1	F
32	44	2	3	F
33	45	2	1	F
34	49	3	4	O
35	51	.	3	U
36	54	1	.	U
37	55	3	4	U
38	56	2	2	U
39	57	2	3	U
40	58	2	1	U
41	59	.	1	U
42	60	3	2	U

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NOTE: F: France, S:Spain, U:US, O:Others

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- Primary efficacy endpoint - All major seizure types

Seizure frequency comparison at each baseline phase, treatment phase (weeks 1-16) and maintenance phase (weeks 7-16) were summarized in Table 2R.

Table 2R. Average weekly seizure counts by seizure type - UK123

	Lamotrigine*		Placebo*		p-val! (WRS)
	min 25th med 75th max	(n)	min 25th med 75th max	(n)	
Baseline					
All major types	16	(78)	14	(89)	.2670
All drop attacks	15	(74)	12	(87)	.7268
Tonic/Clonic seizures	3	(54)	2	(55)	.0423
Treatment (wk1-16)					
All major types	10	(78)	14	(89)	.3216
All drop attacks	7	(74)	11	(87)	.2298
Tonic/Clonic seizures	2	(54)	1	(55)	.6867
Maintenance (wk7-16)					
All major types	9	(74)	13	(84)	.1758
All drop attacks	6	(70)	11	(82)	.0884
Tonic/Clonic seizures	2	(51)	1	(51)	.6453

* Original Seizure counts does not appear to be normally distributed.

! The p-values are for reference only. It is a straight comparison between lamotrigine and placebo without any adjustment.

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Since the normality assumption is violated on the weekly seizure counts, this reviewer performed ANCOVA on $\log_{10}(\text{sz-freq}+1)$, adjust for baseline weekly seizure frequency. The analysis is based on the entire treatment period of week1-16, the intent-to-treat analysis. The results seem to suggest that the treatment effect after adjusted for the baseline weekly seizure counts was statistically significant on all major seizure types ($p=.0014$). Such results for all drop attacks ($p=.0232$) or tonic/clonic seizures ($p=.0397$) were consistent with the findings for the primary efficacy endpoint of all major seizure types (see Table 3R).

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Table 3R. ANCOVA on $\log_{10}(\text{sz-freq})$ adjusted for baseline weekly seizure frequency - UK123

	adjusted treatment effect (SE)	p-value
All Major sz types	-.134 (.04)	.0014
All Drop attacks	-.113 (.05)	.0232
Tonic/Clonic sz	-.100 (.05)	.0397

The median % change in seizure count unadjusted for center was performed by this

reviewer. The results indicated that the median % change in seizure count was significantly higher in the lamotrigine treated group than in the placebo treated group for all major seizure types (32% vs. 9%, p=.003, WRS). The results for each component of the primary efficacy endpoint, i.e., all drop attacks (35% vs. 9%, p=.0052) and tonic/clonic seizures (47% vs. 6%, p=.0237), were consistent with the finding for the primary efficacy endpoint (see Table 4R). It is noted that patients with baseline seizure frequency of 0 were excluded in the analysis.

Table 4R. % change from baseline in seizure count unadjusted for center - UK123

	Lamotrigine					Placebo					p-value (WRS)
	min	25th	med	75th	max (n)	min	25th	med	75th	max(n)	
All Major sz types	-692	-6	31.7	59	96(78)	-935	-19	8.8	39	84(89)	.0030
All Drop attacks*	-1320	-9	35.2	64	100(74)	-3375	-21	9.0	45	97(87)	.0052
Tonic/Clonic sz**	-208	-13	47.0	71	100(54)	-777	-60	5.9	39	100(55)	.0237

* 1 patients in lamotrigine and 1 patient in placebo has baseline seizure frequency of 0.
 ** 6 patients in lamotrigine and 9 patients in placebo has baseline seizure frequency of 0.

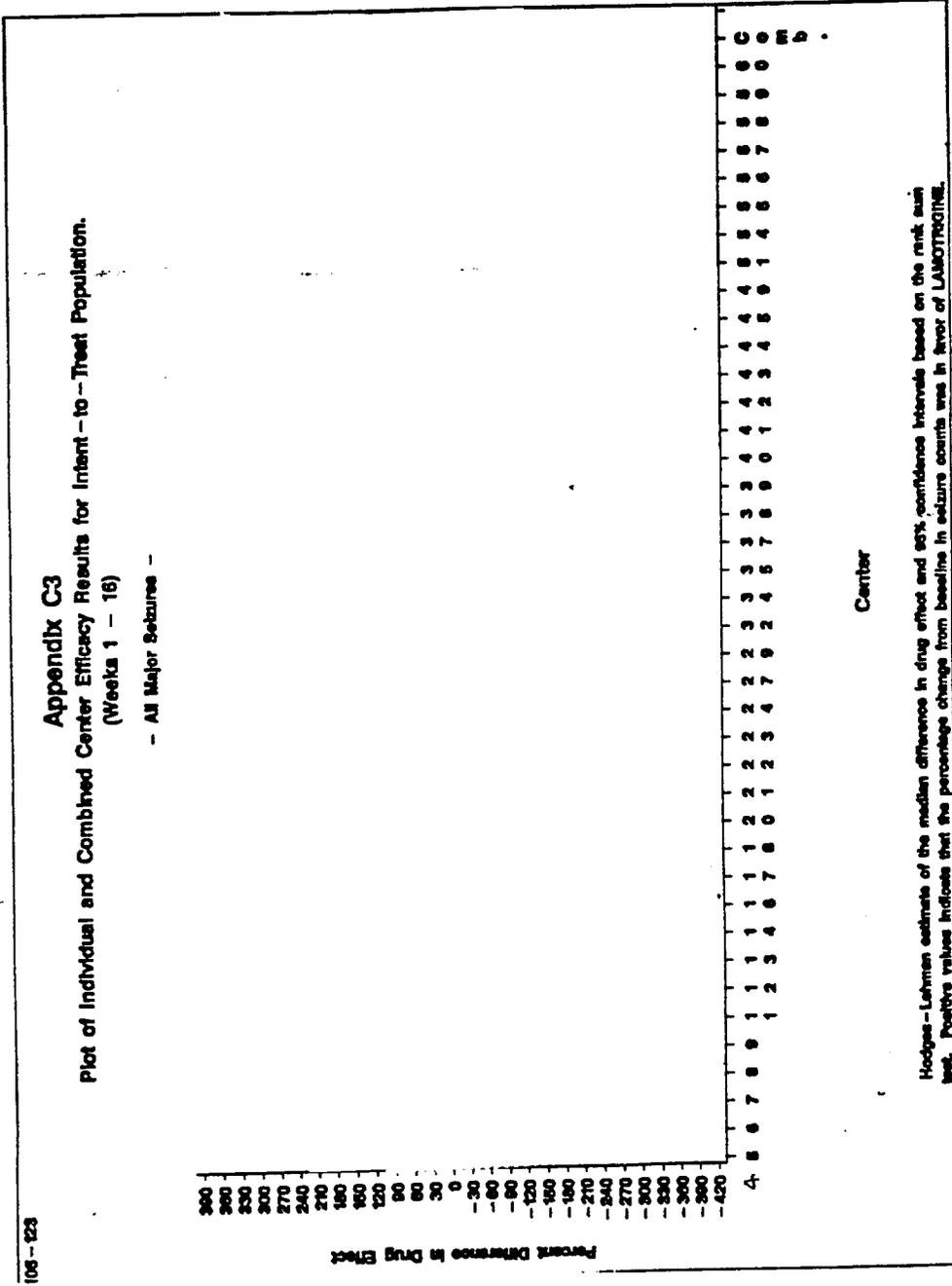
The sponsor performed a nonparametric CMH test adjusting for center on the primary efficacy endpoint of 'all major attacks' as summarized in Table 2S of section 2.1.2. The statistical method actually used by the sponsor is related to but not identical to the one specified in Amendment #7. The sponsor's report stated that 'the power of the CMH test may be increased by first computing the ranks of the percentage change values independent of center (i.e., the Wilcoxon ranks). These Wilcoxon ranks are then used as the response values in the CMH analysis, specifying table scores rather than standardized midranks, in the analysis'. The p-value reported by the sponsor of 0.013 in Table 2S was obtained using the above quoted method. Per telephone conversation with Dr. G. Womble of the sponsor (May 29, 1997), this approach arose from a conversation with Dr. G. Koch, but there was no reference handy.

The analysis method prespecified in amendment #7 is the comparison of the median % change from baseline in all major seizure counts adjusting for the original centers using standardized midrank scores. Here the CMH test is applied to the raw % change data as opposed to the ranks. This reviewer performed the analysis method specified in Amendment #7 which resulted in a p-value of 0.069. It is noted that except for one center having 9 patients, 78% of the centers has at most 5 patients. Using confidence interval as a criterion, 7 centers showed a positive treatment effect, 3 centers showed a negative treatment effect, 10 centers has only one treatment arm with at most 3 patients, and 21 centers cannot reject that the null hypothesis of no treatment difference (see Figure 1S, from p.2700 of vol.28).

An approach to potentially increase the power of detecting a treatment effect is the aligned rank analysis introduced by Hodges & Lehmann (1962) and Koch & Sen (1968). Instead of ranking observations within each center, the raw data were first standardized by location within each center, e.g., sample mean or sample median, then the standardized observations were ranked as a complete set of the aligned observations relative to each other. This reviewer performed two aligned rank tests standardized by sample mean for each stratum, one adjusts for

Figure 15. Plots of Individual and Combined Center Efficacy Results for Intent-to-Treat Population

Appendix C3:



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center and the other adjusts for region. The aligned rank test adjusting for center resulted in a p-value of 0.042 and a p-value of 0.003 when adjustment was made for region.

As a sensitivity check, Table 5R summarizes six approaches for the analysis of % reduction of seizure frequency from baseline. The primary analysis defined by the sponsor was marginally statistically significant (p=.069). The same analysis resulted in a p-value of 0.002 when data were analyzed adjusting for regions. Both aligned rank tests are also statistically significant (p=.042 adjusting for center, p=.003 adjusting for country). The aligned rank tests make the centers more comparable, particularly when the number of patients within a center is small, while maximizing the ability to rank the entire dataset. The WRS test unadjusted for center showed a p-value of 0.003. The ANCOVA on the log-transformed post seizure frequency adjusting for the baseline seizure frequency resulted in a p-value of 0.0014. All six tests indicated that the lamotrigine showed a higher % reduction of seizure frequency from baseline than the placebo.

Table 5R. Results of methods used to compare the % change of seizure frequency from baseline

	unadjusted analysis (WRS)	ANCOVA w/ baseline seizure freq as a covariate	adjusted analysis adjusting for center (Modridit)	adjusted analysis adjusting for region (Modridit)	aligned rank test adjusting for center (table scores)	aligned rank test adjusting for region (table scores)
p-val	.003	.0014	.069	.002	.042	.003

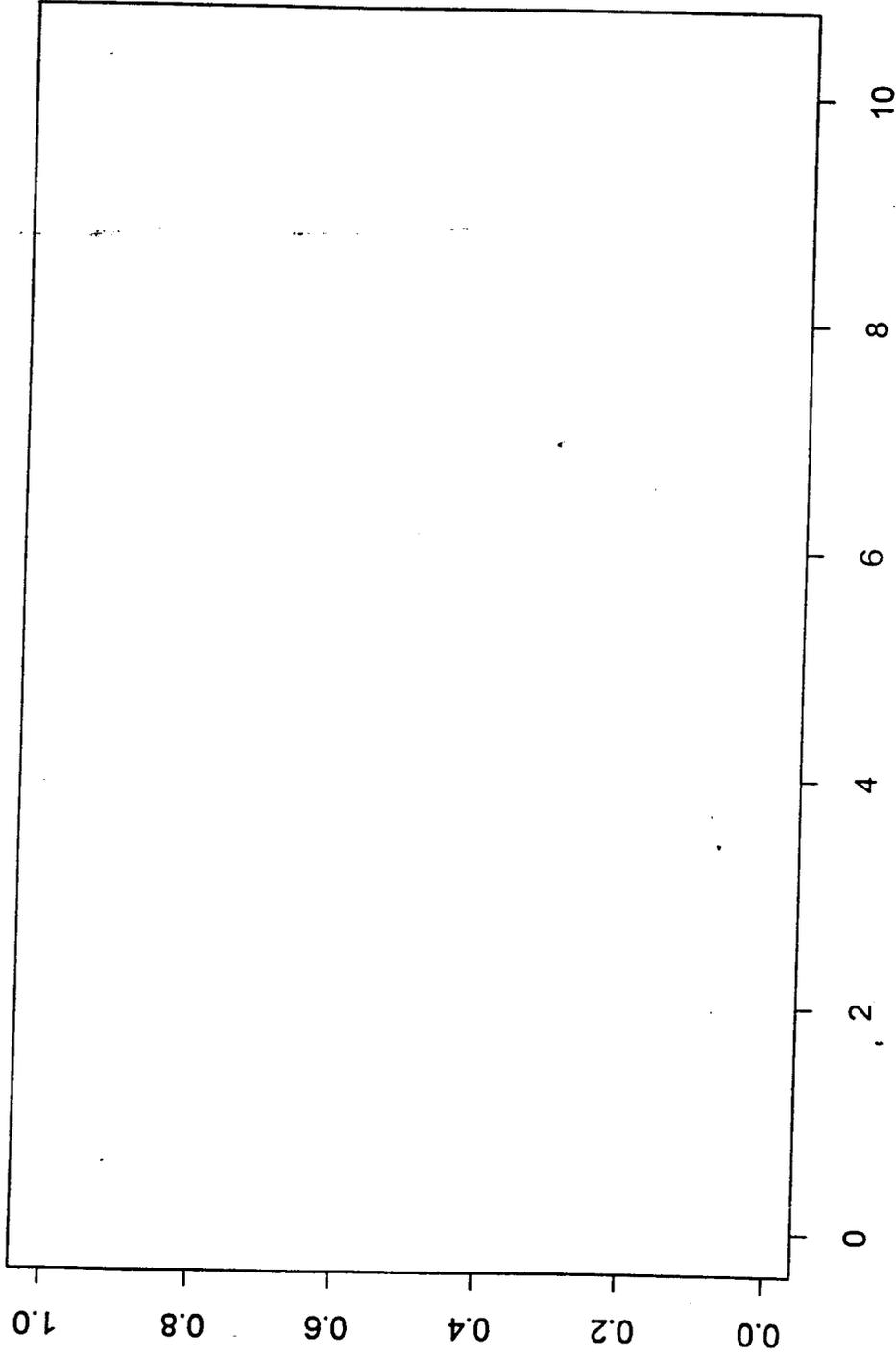
The supplemental results of percentage reduction of seizure frequency from baseline adjusting for regions (pooled centers) were summarized by this reviewer (Table 6R). A consistent pattern of a higher percentage reduction from baseline in lamotrigine treated group than in placebo treated group was shown for all four regions.

Table 6R. The percentage reduction of seizure from baseline by seizure type and by regions

UK123	lamotrigine					placebo				
	min	25th	med	75th	max (n)	min	25th	med	75th	max (n)
All major sz types										
France	-692	-12.5	27.4	59.1	90 (25)	-170	-25	5.0	42	69.2 (34)
Spain	-74.4	36.6	44.2	81.7	96.2 (13)	0	12	25.4	42	68 (12)
US	-14.5	-8.8	48.9	58.6	92.1 (13)	-935	-25	6.7	36	84 (15)
Others	-102	-65	28.8	57.5	73.5 (27)	-480	-24	6.3	41	63 (28)

Figure 1R depicts the empirical cumulative distribution function of post treatment seizure counts reduction in terms of ratio of post-seizure-count to baseline-seizure count between the lamotrigine (solid line) and the placebo (dotted line) treated groups. Lamotrigine treated patients showed fewer seizure counts with greater cumulative probability than placebo treated patients.

Comparison of Empirical cdfs of lamictal and placebo



dotted line is cdf of placebo

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- Seizure days

The endpoint of 'Seizure days' was not in the original protocol. This is considered as a secondary endpoint. The sponsor's results of seizure days analysis support the primary efficacy outcome of all major seizure types.

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ON ORIGINAL

- QOL (ITT)

With ITT analysis, the results of Quality of Life total score scales for seizure severity, behavior, and patient mood showed that there appeared to be more patients having improvement in mood in the lamotrigine group than in the placebo group (51% in lamotrigine group and 30% in placebo group, $p=.007$); there were no differences between treatments in behavior scores ($p=.434$, Fisher's Exact test) or seizure severity ($p=.755$, Fisher's Exact test).

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ON ORIGINAL

- Global evaluations (ITT)

With ITT analysis, the results of the global evaluations assessed by the investigator showed that there were more patients in the lamotrigine group (68%: 53/78) than in the placebo group (39%: 35/89) having marked or some improvement ($p=.0203$). The percentages became 67% (52/78) in the lamotrigine group and 40% (36/89) in the placebo group when evaluated by parent/carer ($p=.066$).

3. Summary and Conclusion

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Trial UK123 is a randomized, double-blind, placebo-controlled, international multicenter clinical trial. Except for one patient in each treatment arm, all randomized patients were used for the efficacy analysis. Except for gender (more males (68% vs. 32%) in the lamotrigine arm and equal numbers of males:females in the placebo arm), there was no major imbalance in either demographic characteristics or neurological history between lamotrigine ($n=79$) and placebo ($n=90$) arms. Required subgroup analyses were provided by the sponsor. For all major seizure types, the baseline median average weekly seizure counts were similar between the lamotrigine treated group and placebo treated group.

The primary analysis defined by the sponsor was marginally statistically significant ($p=.069$). As a sensitivity check, the same analysis resulted in a p-value of 0.002 when data were analyzed adjusting for countries. Both aligned rank tests are also statistically significant ($p=.042$ adjusting for center, $p=.003$ adjusting for country). The WRS test unadjusted for center or country showed a p-value of 0.003. The ANCOVA on the log-transformed post seizure frequency adjusting for the baseline seizure frequency resulted in a p-value of 0.0014. All six tests indicated that the lamotrigine showed a higher % reduction of seizure frequency from baseline than the placebo.

From the Wilcoxon-rank-sum test unadjusted for centers, the median % change in seizure count was significantly higher in the lamotrigine treated group than in the placebo treated group for all major seizure types (32% vs. 9%, $p=.003$). In all four centers, i.e., France, Spain, US, and Others, there was a higher % reduction in the lamotrigine arm than in the placebo arm. The results for each component of the primary efficacy endpoint, i.e., all drop attacks (35% vs. 9%, $p=.0052$) and tonic/clonic seizures (47% vs. 6%, $p=.0237$), were consistent with the findings for the primary efficacy endpoint. The results of ANCOVA on $\log_{10}(\text{sz-freq}+1)$ seem to suggest that the effect of lamotrigine was significant on all major seizure types ($p=.0014$). The results for all drop attacks ($p=.0232$) or tonic/clonic seizures ($p=.0397$) were consistent with the findings for the primary efficacy endpoint of all major seizure types.

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/S/

Sue-Jane Wang, Ph.D. *U*
Mathematical Statistician

Concur: Dr. Sahlroot

/S/ 6/26/97

Dr. Chi

/S/ *for Gary Chi* 6/27/97

cc:

NDA 20-764
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. Tresley
HFD-120/Dr. Feeney
HFD-120/Mr. Purvis
HFD-120/Ms Ware
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Wang
HFD-710/Chron

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SWANG/827-1517/Draft: May 15, 1997

This review consists of 18 pages of text, 2 Sponsor Tables, 1 Sponsor Figure, 6 Reviewer Tables, 1 Reviewer Figure, and 3 Appendices with a total of 21 pages.

Appendix I - inclusion/exclusion criteria, UK123 vol.1.22, p.301
Appendix II - International Classification of Seizures (ICS), UK123
Appendix III. Table 5.12, p.22 of vol.1.47, UK123

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Patients must have a clinical diagnosis of a Lennox-Gastaut Syndrome (severe generalised epilepsy of childhood onset) as defined in the inclusion criteria.

Each patient will be identified by a unique study number.

4.2

Inclusion Criteria at Screen

UK/23

Appendix I

- Patients aged between 3 and 25 years, inclusive, at the start of treatment (patients <15 kg treated with sodium valproate will be excluded).
- Female patients may enter the study if in the judgement of the investigator the patient has no reasonable chance of being/becoming pregnant during the course of the study, based on a review of birth control methods employed and other factors in their gynaecological history.
- Patients with more than one predominantly generalised seizure type including drop attacks (atonic, tonic, major myoclonic) and/or tonic-clonic seizures of at least 1 year duration.
- Age of onset of epilepsy <11 years.
- Seizure Frequency - observable seizures occurring at least every alternate day (or a similar average frequency).
- A recent EEG recording which demonstrates an abnormal background, some slow spike wave abnormality (less than 2.5Hz) and lacks predominantly focal or unifocal abnormalities particularly in younger children.
- Intellectual Function - at least moderate intellectual impairment or a clinical impression of intellectual deterioration in those with normal intellectual function or mild impairment based on results of developmental assessments or IQ tests as appropriate and feasible.
- Antiepileptic medication dosing unchanged for one month before screen.
- The patient and carer (parent or guardian) are likely to comply with all study procedures.
- The carer (parent or guardian) has given written informed consent.

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4.3

Exclusion Criteria at Screen

- Severe known organic disease eg. renal or hepatic impairment which may interfere with drug evaluation.
- Known definite progressive neurodegenerative disorders eg. lysosomal storage disorders, Batten's disease, as established by the appropriate electrophysiological, neuroradiological and metabolic investigations.
- Receiving treatment with more than 2 antiepileptic drugs (additional emergency use of supplementary benzodiazepines is acceptable).
- Previous exposure to lamotrigine.
- Use of investigational (unmarketed) drug within 3 months before screen.
- More than 2 episodes of major tonic-clonic status epilepticus in any month in any of the past 6 months.

4.4

Randomisation Criteria

The following criteria should be fulfilled to enable the patient to enter the double-blind phase of the study:

- The inclusion and exclusion criteria at screen are still satisfied.
- There were no clinically significant abnormalities in the laboratory tests at screen not attributable to enzyme induction by concomitant AEDs.

5.

DRUGS AND DOSAGE

5.1

Study Medication and Randomisation Procedure

Lamotrigine will be provided in the form of white, blackcurrant flavoured, chewable/dispersible tablets of 5, 25 and 100 mg strengths. Placebo tablets identical in appearance, colour and taste will also be provided. Study medication will be given in fixed daily doses of lamotrigine and placebo. The tablets may be chewed or dispersed in a small volume of water (at least enough to cover the whole tablet). The advice for patients and/or parents/carers is given in Appendix A. Patients taking study medication once daily will be instructed to take it in the evening. Medication will be supplied by the Pharmaceutical Development Laboratories, The Wellcome Foundation Ltd., Dartford, in numbered packs containing bottles for dispensing to patients according to the randomisation schedule.

Randomisation numbers will be assigned by selecting the double-blind medication pack corresponding to the next available consecutive number of the appropriate dose schedule. Randomisation numbers will only be assigned

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Appendix II

APPENDIX C: INTERNATIONAL CLASSIFICATION OF SEIZURES¹

A Simple Partial Seizures (Consciousness not impaired)

- 1 With motor signs
 - a focal motor without march A1a
 - b focal motor with march (jacksonian) A1b
 - c Vestibular A1c
 - d Postural A1d
 - e Phonatory (vocalization or arrest of speech) A1e

2 With somatosensory or special-sensory symptoms (simple hallucinations, e.g., tingling, light flashes, buzzing)

- a Somatosensory A2a
- b Visual A2b
- c Auditory A2c
- d Olfactory A2d
- e Gustatory A2e
- f Vertiginous A2f

3 With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation) A3

4 With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures.

- a Dysphasic A4a
- b Dysmnestic (e.g. déjà-vu) A4b
- c Cognitive (e.g. dreamy states and distortions of time sense) A4c
- d Affective (fear, anger, etc) A4d
- e Illusions (e.g. macropsia) A4e
- f Structured hallucinations (e.g. music, scenes) A4f

B Complex Partial Seizures (Generally with impairment of consciousness; may sometimes begin with simple symptomsatology)

- 1 Simple partial onset followed by impairment of consciousness
 - a With simple partial features (A1-A4) followed by impaired consciousness B1a

b With automatisms B1b

2 With impairment of consciousness at onset

- a With impairment of consciousness only B2a
- b With automatisms B2b

C Partial Seizures Evolving to Secondarily Generalized Seizures (GS) (Generalized seizures may be manifested as tonic-clonic, clonic or tonic)

- 1 Simple partial seizures (A) evolving to GS C1
- 2 Complex partial (B) evolving to GS C2
- 3 Simple partial seizures (A) evolving to complex partial seizures (B) evolving to GS C3

D Generalized Seizure (Convulsive or Non-Convulsive)

Generalized seizures are those in which the first clinical changes indicate bilateral involvement of both hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal electroencephalographic patterns bilaterally are bilateral and presumably reflect neuronal discharge which is widespread in both hemispheres.

- 1 (a) Typical Absence² D1a
 - i. Impairment of consciousness only D1ai
 - ii. With mild clonic component D1aii
 - iii. With tonic component D1aiii
 - iv. With tonic component D1aiv
 - v. With automatisms D1av
 - vi. With autonomic components D1avi
 (Mixed forms of D1ai-D1avi may occur and should be documented by using all applicable code numbers).
- 1 (b) Atypical Absence² NO TAG D1b
 - i. Changes in tone that are more pronounced than D1a D1bi
 - ii. Onset and/or cessation that is not abrupt D1bii
- 2 Myoclonic Seizures (myoclonic jerks - single or multiple) D2
- 3 Clonic Seizures D3
- 4 Tonic Seizures D4
- 5 Tonic-Clonic Seizures D5
- 6 Atonic Seizures (astatic; may occur in combination with any of the above generalised seizures) D6

NO TAG
Codes for various subtypes of typical and atypical absence will be used in absence studies only; in all other studies, major codes D1a and D1b may be used.

NO TAG
Based on Publication in Epilepsia 1981; 22: 489-501

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Appendix III

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

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Variable	Treatment Period	Category	Treatment	Weekly Seizure Count				Obs. Median Change in Seizure Count
				N	Median	N	Median	
Sex	Weeks 1 - 16	Female	Lamotrigine	25	14.8	25	11.1	32.7
			Placebo	44	15.2	44	15.1	6.0
	Weeks 7 - 16	Male	Lamotrigine	53	16.8	53	9.3	30.7
			Placebo	45	12.9	45	10.3	12.5
	Weeks 1 - 16	Female	Lamotrigine	25	14.8	25	11.1	33.2
			Placebo	44	15.2	44	14.3	8.7
	Weeks 7 - 16	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	28.4
			Placebo	55	17.0	55	15.3	8.2
	Weeks 7 - 16	> 12 yrs	Lamotrigine	21	14.5	21	6.6	51.0
			Placebo	34	11.0	34	11.7	13.1
	Weeks 1 - 16	<= 12 yrs	Lamotrigine	57	18.5	57	11.1	35.0
			Placebo	55	17.0	55	13.3	12.0
	Weeks 7 - 16	> 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
	Weeks 7 - 16	White	Lamotrigine	73	16.3	73	9.8	30.7
			Placebo	83	15.5	83	14.4	9.3
	Weeks 1 - 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 6.2. Study Design of UK 046

Phase	Duration	Treatment
Baseline	12 weeks	No Medication
Treatment Period 1 (T1)	12 weeks	Placebo or LAMICTAL
Washout Period 1 (W1)	4 weeks	1 week taper (reduction to 50% for 1 week) followed by 3 weeks of placebo
Treatment Period 2 (T2)	12 weeks	LAMICTAL or placebo (crossover from T1)
Washout Period 2 (W2)	4 weeks	1 week taper (reduction to 50% for 1 week) followed by 3 weeks of placebo

Table 6.3. Dosing Regimen – UK 046

Patient Type	Total Daily Dose (mg) ^a		
	Week 1	Weeks 2-12	Week 13
Induced	200	400	200
Balanced	100	200	100
Inhibited	50	75	50

^a patients were instructed to take equal doses at 0900 and 2100 hours

Table 6.4. Study Design of UK 086

Phase	Duration	Treatment
Baseline	4 weeks	No medication
Treatment Period 1 (T1)	18 weeks	Placebo or LAMICTAL
Washout Period 1 (W1)	6 weeks	2 weeks taper (reduction to 50% for 1 week and then to 25% for the second week) followed by 4 weeks of no medication
Treatment Period 2 (T2)	12 weeks	LAMICTAL or placebo (crossover from T1)
Washout Period 2 (W2)	6 weeks	2 weeks taper (reduction to 50% for 1 week and then to 25% for the second week) followed by 4 weeks of no medication

Table 6.5. LAMICTAL Dosing Regimen – UK 086

Patient Type	Total Daily Dose (mg) ^a Treatment Weeks ^b						
	1-4	5	6	7-22	23	24	25-28
Induced	0	29	30	31-46	47	48	49-52
Balanced	0	100	150	200	150	100	0

^a patients were instructed to take doses at 0900 and 2100 hours

^b dependent upon treatment sequence (LAMICTAL/placebo or placebo/LAMICTAL)