

RECEIVED DEC 02 1997

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-241 SE1-003
Applicant: Glaxo-Wellcome, Inc.
Name of Drug: Lamictal Tablets (lamotrigine)
Indication: Use of lamotrigine as monotherapy of partial seizures in adults
Documents Reviewed: Vols. 1.1, 37.5, 37.7, 37.14, 37.21, 37.43-37.45
SAS Database, received April 30, 1997 from Dr. Feeney
Medical Officer: Richard Tresley, M.D. (HFD-120)

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

1 BACKGROUND

In February 1997, Glaxo-Wellcome Inc. submitted a lamotrigine (Trade name: Lamictal tablets) efficacy supplement. This NDA supplement consists of a double-blind conversion trial, which combines two double-blind conversion trials, US30 and US31, into one trial (see amendment #3 in the SUMMARY OF AMENDMENT section) in support of the use of lamotrigine as monotherapy for partial seizures in adult patients.

2 THE PIVOTAL TRIALS

2.1 TRIAL US30

APPEARS THIS WAY
ON ORIGINAL

STUDY DESIGN

This was a multicenter (36 centers), double-blind, parallel, active control comparison of lamotrigine (LTG, target dose 500 mg/d; n=50) to low-dose valproate (VPA, 1000 mg/d; n=64) in adult outpatients with partial seizures refractory to either phenytoin (PHT) or carbamazepine (CBZ). Eligible patients who met entry criteria must have experienced during baseline at least 4 simple partial, complex partial and/or secondarily generalized seizures per 4-week period and have no more than 20 consecutive seizure-free days in order to be eligible for randomization to study medication. The schematic diagram of the study can be found in Figure 1S (Appendix I).

Patients refractory to either PHT or CBZ at 8-week baseline period were randomized to add-on LTG or VPA treatment over a 4-week period. Patients were then converted to monotherapy with LTG or VPA during the next 4 weeks, then continued on monotherapy for an additional 12-week period.

A completed patient was defined as a patient who completed 12 weeks of monotherapy treatment or met one of the "escape" criteria after the initiation of concomitant anti epileptic drug (AED) taper. Escape criteria relative to baseline were: (1) doubling of the average monthly seizure count; (2) doubling of the highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as "a seizure 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. For the "per protocol" analysis, patients who discontinued treatment for reasons other than meeting one of the criteria for "escape" were not counted in the efficacy analysis.

TRIAL OBJECTIVE

The primary objective of the study was to compare the efficacy and safety of LTG monotherapy to VPA monotherapy in adult (≥ 13 years) outpatients with partial seizures. The primary efficacy endpoint defined in the original protocol was "the proportion of patients meeting the "escape" criteria during Study Weeks 13-28 (i.e., beginning the first day of the concomitant AED taper) compared to patients who complete the monotherapy treatment period". The difference in the time to escape patterns between treatment groups was a secondary efficacy endpoint. Secondary objectives were to (1) obtain lamotrigine pharmacokinetics data during add-on treatment, during the withdrawal of concomitant liver enzyme - including AEDs, and during lamotrigine monotherapy; (2) compare the quality of life, seizure severity and the investigator global evaluation with LTG monotherapy to VPA monotherapy; and (3) assess the feasibility of converting to lamotrigine monotherapy from CBZ or PHT monotherapy.

SUMMARY OF AMENDMENTS

The trial began on April 7, 1994 and ended on August 7, 1996. Patient accrual was completed on March 13, 1996. Three amendments were submitted during the trial. Those changes relating to statistical evaluation are summarized. In Amendment#1 (dated and distributed to sites on 28 June, 1994, but submitted to the FDA on 12 September, 1995), there were ten changes. One change concerned study objectives, another data analysis and sample size. Study objectives were modified to include analysis of the Investigator Global Evaluation as a secondary objective (change#10). For data analysis and sample size, the change was "to add a sub-group analysis for patients with secondarily generalized seizures of the primary and secondary efficacy endpoints. A sample size of 42 patients per treatment group is needed to detect a difference with a power of 80% at the .05 level of significance. Seizure types that occurred during Baseline will be monitored, If it is determined that too few patients experience type-C seizures during Baseline, the overall number of patients will be increased

(change#6)." In Amendment#2 (dated and distributed to sites on 20 September, 1994 and submitted to the FDA on 12 September, 1995), there were three changes. With respect to seizure types required for enrollment, the change was "delete the requirement for patients to have at least one uncontrolled secondarily generalized seizure during the 12-week period preceding screening. Patients may still enter this study with any combination of simple partial, complex partial, or secondarily generalized seizures, but they are no longer required to have uncontrolled secondarily generalized seizures". The third Amendment (dated and distributed to sites on 23 May, 1996 and submitted to the FDA on 24 September, 1996) included two changes. Change#1 concerned how the data would be analyzed but no text was revised based on this amendment: "Patient recruitment for Protocol 30 was closed on 13 March, 1996. Data from Protocols 30 and 31, which have identical study designs, will be combined and analyzed as a single study".

STATISTICAL PLAN

Sample size estimation was based on detection of a relative difference of 50% between the two treatment groups (.6 in the LTG arm and .3 in the VPA arm) in the proportion of patients who completed the 12 weeks of monotherapy. It was estimated that at least 42 patients per treatment arm would allow detection of this difference with a power of 80% at the 0.05 level of significance. There was no interim analysis planned. All statistical tests and confidence intervals were two-sided.

For the "per protocol" analysis, the two-tailed Cochran-Mantel-Haenszel test was to be used to assess whether there were statistically significant differences between treatment groups in the proportion of patients meeting the criteria for escape. An intent-to-treat analysis, which includes LTG dropouts as "escape" and VPA dropouts as completers, was also to be done. As a comparative analysis, differences in time-to-escape patterns between treatment groups were compared using the Mantel Rank order statistic (Mantel N. "Evaluation of Survival Data Using Two New Rank Order Statistics Arising in its Consideration" Cancer Chemotherapy Report, 50:163-70, 1966).

2.2 TRIAL US31

The protocol for Trial US31 was identical to Trial US30. For a detailed study description, please see section 2.1.

3 OVERVIEW OF THE RESULTS

Data for studies US30 and US31 were combined prior to breaking the blind of treatment assignment.

A total of 156 patients from 36 clinical centers (38 sites screened patients, 36 sites enrolled patients) were randomized to receive either lamotrigine (n=76) or valproate (n=80). Of those, 114 (50 in LTG and 64 in VPA) patients completed the study, viz., those patients who

completed the monotherapy treatment period or who escaped at any time during the study. Early withdrawal patients not meeting escape criteria were 20 in LTG and 9 in VPA during the treatment transition period and 6 in LTG and 7 in VPA during the monotherapy period. Patient disposition is summarized in Table 1S.

Table 1S. Summary of Patient Accountability (US30/US31) (Table 3. Vol. 5)

Timing Discontinuation	Reason of	LTG	VPA
<u>Randomization - No. of patients randomized (ITT patients)</u>		<u>76</u>	<u>80</u>
During Treatment Transition Period (8-wks)-# patients withdrawn		20(26%)	9(11%)
	Adverse Experience	11	4
	Consent Withdrawn	3	0
	Death	0	1
	Inadequate Resp. (wk 9-12)	3	1
	Inadequate Resp. (wk13-28)	2	1
	Protocol Violation	1	2
Meeting Escape Criteria During Transition Period		15	30
<u>Entering Monotherapy Period - No. of patients</u>		<u>41</u>	<u>41</u>
During Monotherapy Period - No. of patients withdrawn		6(8%)	7(9%)
	Adverse Experience	4	2
	Consent Withdrawn	1	2
	Inadequate Resp.(wk13-28)	0	1
	Protocol Violation	1	2
Meeting Escape Criteria during Monotherapy Period		7	21
Completing Monotherapy Treatment Period		28	13
Completing Monotherapy or Escaping (Per-Protocol Patients)		50	64

The treatment groups were comparable with respect to baseline characteristics and demography. Patients ranged in age from 13 to 73 years. Male:Female ratio was 42:58 for all randomized patients. The treatment groups were also comparable with respect to medical history and seizure etiology. The median baseline seizure frequencies (# of seizures per 4 weeks) were 9 in the LTG group and 10 in the VPA group. Data from individual centers were combined on a geographical basis into four regions, viz., northeast, southeast, midwest, and west.

Primary efficacy endpoint

Three analyses were performed for each efficacy endpoint. 1) Per protocol analysis (50 patients in lamotrigine and 64 patients in valproate): only patients who met escape criteria or completed 12 weeks of monotherapy treatment; 2) ITT analysis : all patients randomized who took at least one dose of study medication, all dropouts were considered as treatment failures; 3) Worst case analysis: all patients who received at least one dose of study medication, lamotrigine

dropouts were considered treatment failures, valproate dropouts were considered completers regardless of why the patients discontinued from the study.

In the per protocol analysis, the proportion of patients completing 12 weeks of lamotrigine monotherapy was more than two and a half times greater than the proportion completing 12 weeks of VPA monotherapy, $p < .001$ after adjustment by region (Table 2S). A statistically significant ($p = .003$) difference in favor of lamotrigine was also apparent in the intent-to-treat analysis. The worst case analysis did not show a significant difference ($p = .890$) between lamotrigine (37%) and VPA (36%) in the proportion of patients completing 12 weeks of monotherapy. The statistical significance seen in the combined study was primarily attributed to study 031 (to be commented on in the Reviewer's Evaluation and Comments section). Figure 2S (Appendix II) depicts differences (with 95% CI) in the proportion of completers from the four regions and the combined study. The most common escape criteria met in both treatment groups were doubling of the highest two day seizure frequency (36% in the LTG group and 39% in the VPA group) and doubling of monthly seizure frequency (36% in the LTG group and 31% in the VPA group).

Table 2S. Results of the adjusted analysis of efficacy data (Tables 11/12 of Vol. 5)

Study	Analysis	LTG n # completing Monotherapy (%)	VPA n # completing Monotherapy (%)	p-value (adj region)	p-value (adj center)
Study 030	Per Protocol	22 11 (50%)	28 7 (25%)	.090	.391
	Intent-to-treat	31 11 (35%)	35 7 (20%)	.179	.504
	Intent-to-treat/worst case	31 11 (35%)	35 14(40%)	.688	.459
Study 031	Per Protocol	28 17 (61%)	36 6 (17%)	.000	.000
	Intent-to-treat	45 17 (38%)	45 6 (13%)	.002	.002
	Intent-to-treat/worst case	45 17 (38%)	45 15 (33%)	.487	.281
Combined	Per Protocol	50 28 (56%)	64 13 (20%)	.000	.001
	Intent-to-treat	76 28 (37%)	80 13 (16%)	.003	.007
	Intent-to-treat/worst case	76 28 (37%)	80 29 (36%)	.890	.752

The sponsor's defined primary efficacy analysis

A completer is defined as a patient who completes 12 weeks of monotherapy treatment or meets one of the "escape" criteria once the AED taper has been initiated. The set of completers comprised the denominator in the per protocol analysis.

Secondary efficacy endpoints

Time to Escape Patterns

In the per-protocol analysis, time to escape (or time to treatment failure) after adjusting for region was significantly longer in the LTG arm (>168 days) than in the VPA arm (57 days), $p = .001$. Time to escape was also longer in the LTG arm than in the VPA arm ($p = .027$) in the intent-to-treat analysis. Treatment failure was synonymous with meeting escape criteria in the per

protocol analysis and was defined as any patient who escaped or dropped out of the study in the intent-to-treat analysis.

Table 3S. Time to treatment failure in days

Population analyzed	Median days to Failure		p-value adjusted by	
	LTG	VPA	center	region
Per protocol	>168*	57	.005	.001
Intent-to-treat	80	58	.060	.027
Worst case	80	64	.246	.324

* The length of the study was 168 days.

Investigator Global Evaluation

The investigator global evaluation was measured by the investigator based on the knowledge of relevant clinical factors (AEs, seizure frequency, etc.) of a patient at the time of evaluation relative to his/her condition at Baseline. The investigator rated the patient's status on a seven point scale. For the statistical analysis, the sponsor grouped all subcategories of deterioration to comprise the deterioration category, and grouped all subcategories of improvement + 'no change' to form the improvement category. There were no differences in the proportions of patients with improvement or no change between the treatment groups at any time point. The sponsor also compared the investigator global evaluation at the last pre-week 30 assessment, i.e., each patient's last on-drug evaluation prior to the follow-up phase. In the per-protocol analysis, the sponsor stated that 'a statistically significant ($p=.019$) difference in favor of LTG was observed in the proportion of patients in each treatment group (66% in LTG and 44% in VPA) with improvement or no change'. In the intent-to-treat analysis, the percentages were 58% in LTG and 47% in VPA ($p=.193$).

Subgroup Analyses

The sponsor reported the results of subgroup analyses on the proportion of patients completing 12 weeks of lamotrigine monotherapy based on baseline AED, gender and race. Analysis by age separated adolescents (age 13 to <18) and the elderly (>59) from adults aged 18-59. Patients taking CBZ at Baseline were compared to those taking PHT. Race was dichotomized as 'white' and 'other'. There were highly significant differences between treatment groups in the proportion of treatment failures in the per protocol and intent-to-treat analysis ($p<.01$) in each subgroup analyzed as shown in Table 4S (see Appendix III). The sponsor stated that 'In general, the subgroup factors of interest did not appear to have an effect on treatment outcome'.

Secondarily Generalized Tonic-Clonic Seizures

There were 38 patients (16 in Study 030 and 22 in Study 031) in the LTG arm and 27 patients (11 in Study 030 and 16 in Study 031) in the VPA arm having secondarily generalized

seizures with the ITT population. All analyses of efficacy data for patients with secondarily generalized seizures revealed no statistically significant differences between the treatment groups with per-protocol (48% in LTG vs. 32% in VPA, $p=.298$), intent-to-treat (29% in LTG vs. 26% in VPA, $p=.747$), and worst case analyses (29% in LTG vs. 44% in VPA, $p=.211$).

4 REVIEWER'S EVALUATION AND COMMENTS

In this NDA submission, the sponsor combined two studies (US30 and US31) into one study due to slow accrual. The decision of pooling two studies into one trial was discussed with and agreed to by the Agency before the accrual ended (amendment#3).

Primary Efficacy Endpoint

Table 1S cannot be reproduced by this reviewer using the sponsor's original electronic submission. This reviewer requested the sponsor, via fax dated Aug. 26, 1997, to explain the discrepancies between the electronic file and the sponsor Table on patient accountability. According to the sponsor's response, dated Sept. 4, 1997, the discrepancies were caused by correction needed after the database was frozen. Two patients accounts for the discrepancies:

Patient 030-001-01040 was a LTG patient who after the database was frozen was discovered to have met escape criteria. Unable to change the raw database, the sponsor hardcoded the information into their analysis database. The patient met the "Doubled Two-Day-Seizure-Frequency" on 01Jun95.

Patient 031-0009-09065 was VPA patient who had a reason for escape listed and an escape date given in the electronic file, but did not have the "Met Escape Criteria" field marked YES. The sponsor's SAS code categorized this patient as an escaper.

Sponsor later submitted another electronic file including all the relevant dates needed so that this reviewer can check the computational algorithm of weeks for calculating the timing of the discontinuation. Table 1S is now confirmed by this reviewer.

From Table 2S (see section 3) of the sponsor, both the intent-to-treat analysis and the per-protocol analysis showed that Study US31 is a positive study whereas Study US30 failed to show a statistically significant treatment effect on the proportion of patients completing the 12-week monotherapy. The p-values presented by the sponsor are results after adjusting by region or after adjusting for center. The protocol specified that the Cochran-Mantel-Haenszel test would be performed, but did not state whether center or region would be the stratification factor. Although center or region is a natural choice for stratification, since the sample size is small for a majority of the centers, the stratified analysis might not be more powerful than the unadjusted analysis. This reviewer performed two additional analyses. One consisted of two treatment group comparisons without center adjustment. The other is the trial-stratified analysis.

Table 1R Results of the unadjusted analysis of primary efficacy endpoint*

Study	Analysis	LTG	VPA	p-value (unadj)
Study 030	Per-Protocol	50%(11/22)	25%(7/28)	.068
	ITT	35%(11/31)	20%(7/35)	.159
	ITT/worst case	35%(11/31)	40%(14/35)	.706
Study 031	Per-Protocol	61%(17/28)	17%(6/36)	.001
	ITT	38%(17/45)	13%(6/45)	.008
	ITT/worst case	38%(17/45)	33%(15/45)	.660

* unstratified by center

Table 1R summarizes the results of the primary efficacy endpoint, viz., % of patients completing 12 weeks of LTG monotherapy without center or region adjustment. The unadjusted results shown in Table 1R are consistent with the region-adjusted or study-by-center adjusted analysis shown in Table 2S. That is, there was no statistically significant difference in the % of patients completing 12 weeks of LTG monotherapy in US30, either by per-protocol (p=.068), ITT (p=.159), or ITT/worst-case (p=.706) analysis. The statistically significant treatment effect was seen in US31, either in the per-protocol (p=.001) or the ITT (p=.008) analysis, but not in the ITT/worst-case (p=.660) analysis. All 36 centers across both trials (17 centers in US30 and 19 centers in US31) were small except 2 centers in US30 (030-0003, 030-0015) and 5 centers in US31 (031-0009, 031-0014, 031-0015, 031-0017, 031-0023) with at least four or more patients per treatment arm. Among these 7 centers, center 030-0003 from study 030 [67% (4/6) in LTG vs. 17% (1/6) in VPA] and center 031-0023 from study 031 [75% (6/8) in LTG vs. 13% (1/8) in VPA] each showed that 95% CI of the % completing 12 weeks of LTG monotherapy is greater than zero. The remaining 5 centers showed that 95% CI contains the zero.

Basic demographics were similar between studies US30 and US31. The median age at screening was 35-yr in US30 and 36-yr in US31. About 60% of the patients were females in each trial. The majority of the patients (67%) were white in each trial. The percentages of patients with secondarily generalized seizures at baseline were 52% (LTG) vs. 31% (VPA) in study US30 and 49% (LTG) vs. 36% (VPA) in study US31. Concomitant AEDs at baseline was slightly imbalanced in US30 (77% in LTG vs. 54% in VPA had CBZ as the AED at screening, p=.049), but not in US31 (53% in LTG vs. 60% in VPA).

The protocols were identical for US30 and US31. If there were any differences in the trial conduct, it would likely be either incomparable study populations implied by the differences in baseline demographics or baseline clinical characteristics, or different administration of the treatment. This reviewer performed an analysis stratified by 'Study' to account for potential different characteristics that were latent during the process of treatment administration. The results of the stratified analysis indicated that the % of patients completing 12 weeks of LTG monotherapy after adjusting for potential heterogeneity between the two trials was statistically

significant for the per-protocol analysis ($p=.001$) and for the ITT analysis ($p=.004$), not for the ITT/WC analysis ($p=.932$). In addition, to account for potential imbalance on concomitant AED use at screening, two sensitivity analyses were performed by this reviewer: an analysis stratified by concomitant AED use and an analysis stratified by protocolxAED use at screening. The results were consistent with the analysis stratified by protocol alone in terms of statistical significance.

The sponsor combined data from individual centers on a geographical basis into four regions, viz., northeast, southeast, midwest, and west. The analysis results based on the combined study (US30 and US31) reported by the sponsor and the analysis results based on the analysis stratified by 'Study' reported by this reviewer are in good agreement. Although study US030 failed to reach statistical significance, the pooled results and the stratified results accounting for potential heterogeneity of the trials each showed the overall statistical significance of the treatment effect in terms of % of patients completing 12 weeks of LTG monotherapy, the primary efficacy outcome variable.

It is noted that the statistically significant results in the analyses of the primary efficacy endpoint, adjusted or unadjusted for region or stratified by study, were from the per-protocol or the ITT analysis. The ITT/WC analysis which failed to show statistical significance, was based on the worst case scenario representing the conservative approach in favor of VPA. The conservativeness is shown in Table 1S (section 3). Early withdrawal patients were more than twofold (26% vs. 11%) in LTG treated patients compared to VPA treated patients during the treatment transition period (8-week). Most withdrawals were due to adverse experiences (55% in LTG vs. 44% in VPA). The overall withdrawal in the LTG arm (34%), including those withdrawn during the monotherapy period, was 1.5 times higher than that in the VPA arm (20%). Adverse experience was the primary reason for early withdrawal during the trial. Of those withdrawn, 58% in the LTG group and 38% in the VPA group withdrew due to adverse experiences. It appeared that patients dropped for safety reasons over efficacy reasons. Thus, the ITT/WC analyses might be too conservative.

The medical reviewer was interested in the number and outcomes of patients who entered the monotherapy treatment period. The rationale was the performance of this subset of patients may be affected by the speed of dose escalation (4-week) and deescalation (4-week) during their transition period. From Table 1S, 41 (54%) of 76 LTG patients entered the 12 weeks monotherapy. Conditioning on patients who completed the transition period, there was a twofold increase in the % completing the 12-week monotherapy treatment period in LTG treated patients (68%) as compared to VPA treated patients (32%). This pattern is in parallel with the intent-to-treat analysis.

Time to Escape Patterns

The results on time to escape by either per-protocol, ITT, or ITT/WC analyses reported by the sponsor (Table 3S of section 3) were verified by this reviewer. Time to treatment failure was

synonymous with meeting escape criteria in the per protocol analysis, and was defined as any patient who escaped or dropped out of the study in the intent-to-treat analysis. The median time to treatment failure was longer in the LTG arm (11.6 wks; 95%CI: 8 wks - 20.3 wks) than in the VPA arm (8.4 wks; 95% CI: 7.9 wks - 10.6 wks) with the ITT analysis ($p=.027$). The result of the per-protocol analysis ($p=.001$) was consistent with the ITT analysis, but not the ITT/WC analysis ($p=.324$).

5 SUMMARY AND CONCLUSION

The trial was designed to study lamotrigine from add-on therapy during and after conversion to monotherapy in adult patients with partial seizures. Due to slow accrual, the sponsor requested a conference with the Agency on 2/29/96. At that time, patient recruitment since trial commencement was approximately 50% of the targeted sample size. The Agency stated that a single pivotal efficacy study for monotherapy application was acceptable since the anticonvulsant efficacy of lamotrigine had been established in add-on trials submitted as part of the original NDA 20-241. The Agency agreed that combining data from US30 and US31 and analyzing these data as a single study was acceptable. The sponsor closed accrual on 3/13/96. Studies US30/US31 were combined and a single analysis was performed on the results.

The primary efficacy endpoint, the % of patients completing 12 weeks of LTG monotherapy, was statistically significant in Study 031 with the unadjusted, center-adjusted, region-adjusted, or AED-adjusted analyses in either per-protocol patients or intent-to-treat patients. Statistical significance was not reached in Study 030. The sponsor's analysis of the combined studies, either adjusting for center or adjusting for region, showed statistical significance. The analysis stratified by 'Study' reported by this reviewer also showed statistical significance. The results of this reviewer's analysis stratified either by baseline AED or by StudyxAED also showed statistical significance. In addition, the secondary efficacy endpoint of time to escape pattern showed a longer time to treatment failure in favor of LTG. The significance was shown in the per-protocol and ITT analyses, but not the ITT/worst-case analysis.

The ITT analysis is reasonable in that dropouts were considered as treatment failures. Early discontinued patients were treated equally between the LTG and the VPA arms in terms of treatment efficacy. However, when most early discontinuations were due to safety as opposed to lack of efficacy, the ITT/WC analyses might be too conservative because most withdrawals are LTG patients which were considered treatment failures in the analysis. VPA dropouts were considered as completers regardless of why the patients discontinued from the study.

Overall, there is statistical evidence from the intent-to-treat analysis that adult patients with partial seizures refractory to either CBZ or PHT receiving LTG completed the 12-week monotherapy at a higher rate than those patients receiving VPA. A secondary efficacy endpoint, longer time to treatment failure, supports the finding of the primary endpoint.

APPEARS THIS WAY
ON ORIGINAL

/S/

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur:

for

Dr. Sahlroot

/S/

11-14-97

Dr. Chi

/S/ 11/2/97

cc:

NDA 20-241 SE1-003
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

APPEARS THIS WAY
ON ORIGINAL

SWANG/827-1517/Draft: October 16, 1997/LAM_EF.WPD

This document consists of 11 pages of text (3 tables from the sponsor, 1 table from this reviewer), 3 appendices, with a total of 14 pages.

Appendices:

Figure 1S. Study schema

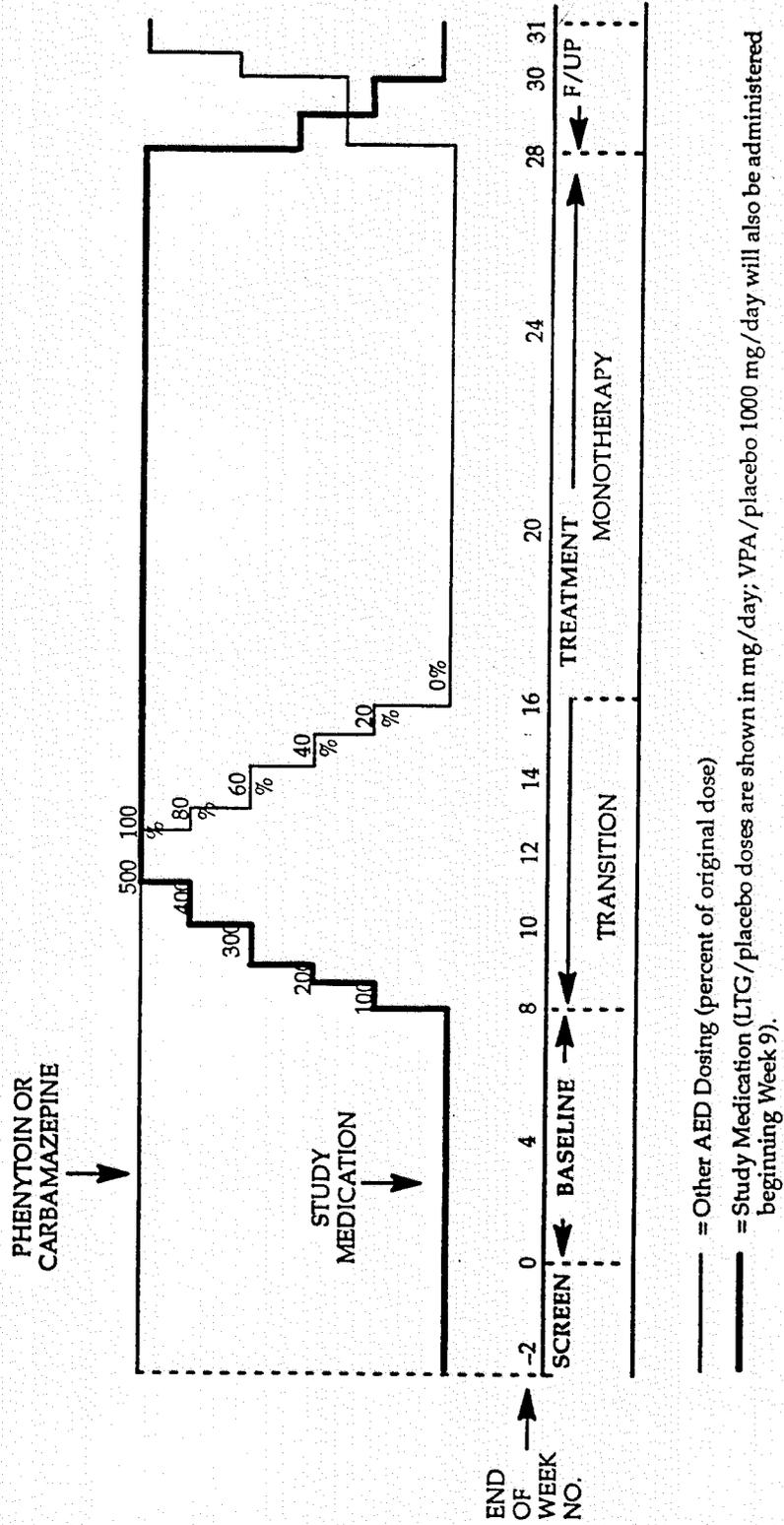
Figure 2S. Estimated treatment effect with 95% CI of the primary efficacy endpoint by 4 regions and combined

Table 4S. Results of subgroup analysis

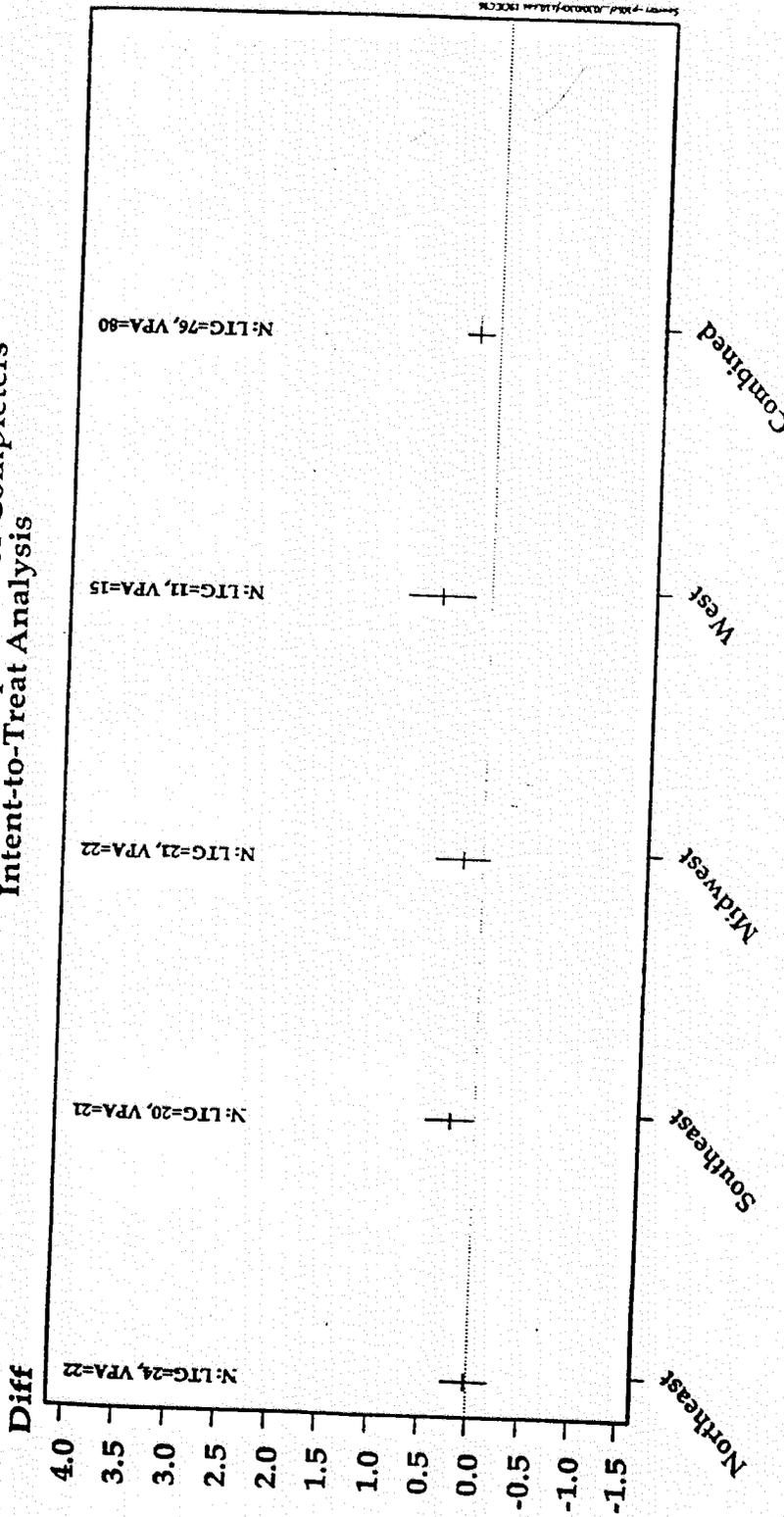
Appendix I

Figure 1. Schematic Diagram of Study

Figure 1S.



Appendix II (Figure 2S)
 Individual and Combined Region Plot
 of the Difference in Proportion of Completers
 Intent-to-Treat Analysis



Difference in mean proportions with 95% CI based on normal approximation to binomial. Positive values indicate that the difference in proportions was in favor of LAMICTAL.

BEST POSSIBLE COPY

Project 105c-030
(Data as of: November 27, 1996)

Table 4S

Results of Per Protocol and Intent-to-Treat Subgroup Analysis of Efficacy Data
Table 23 (Appendix III)

96b5(030efs05) 19DEC96 12:17

Analysis	Strata	Category	LAMICTAL			VPA			P-Value (Adjusted for Region and Strata)	P-Value (Breslow-Day)	
			No. Pts.	No. Completers	No. Failures	No. Pts.	No. Completers	No. Failures			
Per Protocol	Age	13-<18	3	2 (67%)	1 (33%)	2	0 (0%)	2 (100%)	0.000	0.201	
		18-59	46	25 (54%)	21 (46%)	13	0 (0%)	46 (78%)			
		>59	1	1 (100%)	0 (0%)	3	0 (0%)	3 (100%)			
		Baseline AED	CBZ	30	20 (67%)	10 (33%)	39	8 (21%)	31 (79%)	0.000	0.290
			PHT	20	8 (40%)	12 (60%)	25	5 (20%)	20 (80%)		
		Race	Other	18	11 (61%)	7 (39%)	18	5 (28%)	13 (72%)	0.000	0.258
			White	32	17 (53%)	15 (47%)	46	8 (17%)	38 (83%)		
		Sex	Female	25	14 (56%)	11 (44%)	40	9 (23%)	31 (78%)	0.000	0.445
			Male	25	14 (56%)	11 (44%)	24	4 (17%)	20 (83%)		
	Intent-to-Treat	Age	13-<18	5	2 (40%)	3 (60%)	2	0 (0%)	2 (100%)	0.005	0.204
		18-59	68	25 (37%)	43 (63%)	74	13 (18%)	61 (82%)			
		>59	3	1 (33%)	2 (67%)	4	0 (0%)	4 (100%)			
		Baseline AED	CBZ	48	20 (42%)	28 (58%)	46	8 (17%)	38 (83%)	0.003	0.669
			PHT	28	8 (29%)	20 (71%)	34	5 (15%)	29 (85%)		
		Race	Other	24	11 (46%)	13 (54%)	25	5 (20%)	20 (80%)	0.005	0.410
			White	52	17 (33%)	35 (67%)	55	8 (15%)	47 (85%)		
		Sex	Female	43	14 (33%)	29 (67%)	48	9 (19%)	39 (81%)	0.003	0.221
			Male	33	14 (42%)	19 (58%)	32	4 (13%)	28 (88%)		
Intent-to-Treat/WC		Age	13-<18	5	2 (40%)	3 (60%)	2	0 (0%)	2 (100%)	0.999	0.070
		18-59	68	25 (37%)	43 (63%)	74	28 (38%)	46 (62%)			
		>59	3	1 (33%)	2 (67%)	4	1 (25%)	3 (75%)			
		Baseline AED	CBZ	48	20 (42%)	28 (58%)	46	15 (33%)	31 (67%)	0.801	0.128
			PHT	28	8 (29%)	20 (71%)	34	14 (41%)	20 (59%)		
		Race	Other	24	11 (46%)	13 (54%)	25	12 (48%)	13 (52%)	0.878	0.027
			White	52	17 (33%)	35 (67%)	55	12 (48%)	13 (52%)		

NOTES: In the Per Protocol Analysis, failure is defined as any patient who escaped. In the Intent-to-Treat Analysis, failure is defined as any patient who escaped or withdrew from the study. In the Intent-to-Treat/Worst Case Analysis, for LTG patients, failure is defined as any patient who escaped or dropped out of the study. For VPA patients, failure is defined as any patient who escaped.

P-Values are adjusted for region and strata.

APPEARS THIS WAY
ON ORIGINAL

TO: Gilda Womble, Ph.D.
Statistician

THROUGH: Elizabeth A. McConnell, Pharm.D.
Project Director,
Regulatory Affairs
Glaxo Wellcome Inc.

FAX: 1-919-483-5118 / 1-919-315-0832

FROM: Sue-Jane Wang, Ph.D., /S/
Mathematical Statistician
Division of Biometrics I, CDER, FDA

Date: August 25, 1997

RE: Discrepancy of Table 3 in Volume 5 of NDA 20-241 SE1-003

Dear Dr. Womble,

Patients accountability summarized in Table 3 of volume 5 for Lamictal monotherapy NDA submission (20-241 SE1-003) does not match with the electronic submission of 'sta.sd2'. Please explain and resolve the discrepancies. Examples of discrepancy are (1) # of patients meeting escape criteria were 21(LTG):50(VPA) in sta.sd2, but were 22(LTG):51(VPA) in Table 3 of volume 5, (2) # of patients completing monotherapy period were 29(LTG):13(VPA) in sta.sd2, but were 28(LTG):13(VPA) in Table 3 of volume 5.

When you resubmit this table, please provide (i) the correct electronic file of sta.sd2, (ii) individual trial summary and (iii) the combined summary (US30 and US31) as presented in Table 3 of Volume 5. In particular, please include 'the computational algorithm of weeks' so that the actual week number and the corresponding period (transition period or monotherapy period) for each of the event occurred can be properly captured in the electronic data file, e.g., adverse experience occurred at day 44 since initial treatment, equivalently, week 6.3, in taper transition period. In addition, please include date last seen for each patient.

Please submit the SAS log and SAS output of the analyses for the correct electronic data file at your earliest convenience in order to expedite the review process.

Thank you.

CC: HFD-120/Division File
HFD-120/Richard Tresley, M.D.
HFD-710/Todd Sahlroot, Ph.D.
HFD-120/Jackie Ware, CSO