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APPLICATION NUMBER: 020241/S003 AND 020764/S001

STATISTICAL REVIEW(S)

RECEIVED FEB 20 1998

UPDATE OF ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

NDA#: 20-241 SE1-003
 Applicant: Glaxo-Wellcome, Inc. FEB 18 1998
 Name of Drug: Lamictal Tablets (lamotrigine)
 Indication: Use of Lamotrigine as monotherapy of partial seizures in adults
 Documents Reviewed: Medical reviewer's Assessment & electronic database
 Medical Officer: Richard Tresley, M.D. (HFD-120)

The following results are additional analyses requested by the medical review team as a further update of the addendum to statistical review and evaluation dated 01-16-98.

Table 1. The sponsor's NDA submission on patients' status of escape, withdrawal, and completer

Arm	Esc	With- drawal	Inadequate response			Other withdrawal patients			Completer	Total
			transition		mono- therapy	transition*		mono** therapy		
			<13wk	≤16wk		<13wk	≤16wk			
LTG	22	26	3	2	0	13	2	6	28	76
VPA	51	16	1	2	0	4	2	7	13	80

* Other withdrawn patients - transition: patients who didn't complete the transition period.

** Other withdrawn patients - monotherapy: patients who didn't complete the monotherapy period.

Note: after patients' withdrawal, they were in the follow-up period, then, they were terminated from the study. The maximum time between follow-up date and termination date was 2 months.

Table 2. The medical reviewer Dr. Richard Tresley's assessment on patients' status by 02/03/98

Arm	Escape	Withdrawal	Inadequate response	Other Withdrawal**		Completer	Total
				transition	monotherapy		
LTG	27	21	5 3(<13wk) 2(>13wk)	14 10AE 3CW 1PV	2 2AE	28	76
VPA	52	15	3 1(10wk) 2(16wk)	7 4AE 2PV 1D	5 2AE 2CW 1PV	13	80

Reasonable analysis - classification of escape is based on the reason of withdrawal:

- 1) inadequate response is considered as escape
- 2) 5 more LTG and 1 more VPA were assigned as escape after the medical reviewer's assessment on CRF of adverse event (AE), consent withdrawn (CW), protocol violation (PV), death (D) withdrawn patients (02/03/98, see attachment), the telecon with the sponsor regarding the interpretation of the 'follow-up period' (02/02/98).

Worst case type Analysis

use 1) and 2) above, the remaining withdrawal patients (WD, WDT, AE) were assigned as escape for LTG and non-escape for VPA depending on specific escape categories.

Table 3. Reviewer's analysis results based on the Medical Reviewer's assessment on CRF**

Escape category	Reasonable Analysis (ITT)			Worst Case Type Analysis (ITT)		
	LTG % escape	VPA % escape	p-val*	LTG % escape	VPA % escape	p-val*
E+I	42%(32/76)	69%(55/80)	.0012	----	----	----
E+I+WD	63%(48/76)	84%(67/80)	.0038	63%(48/76)	69%(52/80)	.5014
E+I+WDT	61%(46/76)	78%(62/80)	.0248	61%(46/76)	69%(52/80)	.3168
E+I+AE	58%(44/76)	76%(61/80)	.0263	58%(44/76)	69%(52/80)	.1848

** patients' escape status were assessed by the medical reviewer blinded to the treatment assignment.
 *Fisher's Exact test; E: Escape; I: Inadequate response; WD: other withdrawal; WDT: other withdrawal-transition only; AE: adverse event.

It appeared that the results of escape analyses showed statistically significant difference between LTG and VPA (p<.05) from all reasonable analyses explored. The reasonable analysis defines a patient's escape status based on the withdrawal reason of interest irrespective to patients' treatment assignments. On the other hand, the results of worst case type analyses failed to show a significantly lower % of escape for LTG as compared to VPA, p-value ranges from

Per medical review team's request, the following summarizes those patients who either escaped or withdrew around week-13:

- Among the escape patients, two patients had escape-date the same as AED-taper-date during the transition period (LTG, 031-0006-06153; VPA 031-0011-11037), and two patients had AED-taper-date missing (VPA, 031-0014-14054, first-date-transition 4/6/95, last-date-transition 5/7/95, escape-date 5/4/95; VPA, 031-0014-14074, first-date-transition 5/2/95, last-date-transition 5/29/95, escape-date 5/30/95). It appeared that these four patients had their escape-date occurred approximately 4-weeks after the first-date-transition which is either the ending of week-12 or the beginning of week-13. The

remaining escape patients had the escape-dates later than their AED taper-dates.

- Among the four inadequate response patients, two patients withdrew at the end of week-10 and the beginning of week-11 (LTG, 031-0014-14076, first-date-transition 06/06/95, last-date-transition 06/19/95, follow-up-date 06/20/95; LTG, 031-0015-15013, first-date-transition 08/10/94, last-date-transition 08/24/94, follow-up-date 08/25/94) and two patients withdrew at week-12 (LTG, 030-0025-25165, first-date-transition 01/31/96, last-date-transition 02/26/96, follow-up-date 02/27/96; VPA, 031-0020-20173, first-date-transition 03/06/96, last-date-transition 03/29/96, follow-up-date 03/30/96).

Table 4 summarizes the results of escape analyses where patients withdrawn before week-13, i.e., during titration period, were considered as non-escapes. Similar results are found between Table 3 and Table 4. That is, variations of reasonable analyses showed statistical significance whereas variations of worst case type analyses failed to show statistically significant difference in % of escape between the LTG arm and the VPA arm.

Table 4. Reviewer's analysis results based on the Medical Reviewer's assessment on CRF where patients withdrew before week-13 was considered as non-escape**

Escape category	Reasonable Analysis (ITT)			Worst Case Type Analysis (ITT)		
	LTG % escape	VPA % escape	p-val*	LTG % escape	VPA % escape	p-val*
E+I	38%(29/76)	68%(54/80)	.0004	----	----	----
E+I+WD	59%(45/76)	83%(66/80)	.0015	59%(45/76)	68%(54/80)	.3202
E+I+WDT	57%(43/76)	76%(61/80)	.0110	57%(43/76)	68%(54/80)	.1876
E+I+AE	54%(41/76)	75%(60/80)	.0073	54%(41/76)	68%(54/80)	.1013

** patients' escape status were assessed by the medical reviewer blinded to the treatment assignment.

*Fisher's Exact test; E: Escape; I: Inadequate response; WD: other withdrawal; WDT: other withdrawal-transition only; AE: adverse event.

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NDA 20-241 SE1-003

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SWANG/827-1517/Draft: February 3, 1998/Lam_mono.ad2

This document consists of 4 pages of text, 1 attachment, 1 tables from the sponsor, 1 table from the medical reviewer, and 2 tables from this reviewer, with a total of 5 pages.

Attachment: Medical reviewer's assessment 02/03/98

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RECEIVED JAN 26 1998

ADDENDUM TO THE STATISTICAL REVIEW AND EVALUATION

NDA#: 20-241 SE1-003

Applicant: Glaxo-Wellcome, Inc. JAN 16 1998

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)

This is an addendum to the original statistical review and evaluation dated Dec. 2, 1997. The following review has been discussed with the medical review team and Biometrics team leader.

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 in support of the use of lamotrigine as monotherapy for partial seizures in adult patients.

CONCERNS ABOUT THE PRIMARY EFFICACY ENDPOINT

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 sponsor stated that "Study 30/31 used a study design which was similar to one used to demonstrate the efficacy of felbamate monotherapy in the treatment of partial seizures" in p.169 of vol. 5. The primary efficacy endpoint for the two felbamate monotherapy trials (protocols 244 and 284) was escape from therapy. However, the primary efficacy endpoint defined for lamotrigine contains two components: (1) the proportion of patients meeting the "escape" criteria during Study Weeks 13-28 (i.e., beginning the first day of the concomitant AED taper), and (2) the proportion of patients completing the monotherapy treatment period.

The interpretation and analysis of the primary efficacy endpoint is ambiguous in the presence of dropouts. Each patient is classified as a completer (completing 12 week monotherapy

period), an escape (meeting predefined escape criteria), or a withdrawal. With the above defined primary efficacy endpoint, a completer or an escape can be classified without ambiguity. However, a withdrawn patient becomes problematic. For the protocol defined primary efficacy endpoint analysis purpose, should a withdrawn patient be classified as an escape for component (1) of the primary efficacy endpoint or a completer for component (2) of the primary efficacy endpoint? The question is how early withdrawn patients are classified.

From Trial US30/31, the % of premature withdrawn were moderate (20%) in the VPA group and high (34%) in the LTG group. When these %s were summarized by Trials (Table 1R for Trial 30 and Table 2R for Trial 31), it appeared that the % of patients withdrawn early was one and a half time greater in the LTG arm (29%) compared to the VPA arm (20%) in Trial 30 and two-fold greater in the LTG arm (38%) compared to the VPA arm (20%) in Trial 31. Trial 31 had higher early withdrawal rate and reached statistical significance for the ITT completer analysis whereas Trial 30 had similar early withdrawal rates between the two arms and failed to reach statistical significance for the ITT completer analysis (see Appendix). Note that in the ITT completers analysis, withdrawals were classified as non-completers.

Table 1R. Distribution of patients in completer, escape, and withdrawal (US30) electronic data

US30	Complete Mono-therapy	Escape (wk13-28)			Withdrawn (wk13-28)			total
		Trans. wk13-16	Mono. wk17-28		Trans. wk13-16	Mono. wk17-28		
LTG	11 (35.5%)	11 (35.5%)	6	5	9* (29%)	7	2	31
VPA	7 (20%)	21 (60%)	12	9	7* (20%)	3	4	35

* Among the LTG AE withdrawn patients (n=7), one met escape criteria, one had missing diaries; Among the VPA AE withdrawn patients (n=3), one met escape criteria.

Table 2R. Distribution of patients in completer, escape, and withdrawal (US31) electronic data

US31	Complete Mono-therapy	Escape (wk13-28)			Withdrawn (wk13-28)			total
		Trans. wk13-16	Mono. wk17-28		Trans. wk13-16	Mono. wk17-28		
LTG	17 (38%)	11 (24%)	7	4	17* (38%)	13	4	45
VPA	6 (13%)	30 (67%)	15	15	9 (20%)	6	3	45

* Among the LTG AE withdrawn patients (n=8), two met escape criteria, 2 had missing diaries.

If the focus is completers, the sponsor's ITT/WC analysis, which considers withdrawn patients and escaped patients in the LTG arm as non-completers and in the VPA arm as

completers, might be too conservative. On the other hand, if the focus is escapes, efficacy comparison may be biased without proper classification of early dropouts who no longer have a chance to demonstrate whether lamotrigine is effective or not.

Because of the substantial dropout rates seen in the US30/31, methods of classification of the withdrawn patients will affect the trial results. The medical reviewer (Dr. Tresley) reviewed, while blinded to the treatment assignment, the case report forms for those patients who withdrew early due to adverse experience (AE), viz., the major reported reason of early withdrawal. The objective was to consider a reasonable assessment of the efficacy status of these withdrawn patients for a reasonable worst case analysis.

MEDICAL REVIEWER'S ASSESSMENT

The Medical Reviewer's assessment can be found in the Results Section of Outcome Measures (p.9-p.12) of the Clinical Review. Three LTG patients (030-0001-01038, 031-0006-06046, and 031-0026-26161) who withdrew due to adverse experience were found to meet efficacy escape criteria earlier in the study. Inadequate documentation of seizure diaries occurred in 3 additional LTG patients (030-0015-15017, 031-0014-14026, and 031-0017-17041) and one VPA patient (030-0015-15074). This amounts to 2/7 in the LTG arm and 1/3 in the VPA arm for Trial 030 and 4/8 in the LTG arm and 0/3 in the VPA arm for Trial 031 misclassification. For a reasonable worst case escape analysis, the medical review team considered any patients withdrawn from the VPA arm and those patients withdrawn due to AE from the LTG arm as withdrawals or non-escapes, and the remaining LTG withdrawn patients as escapes.

STATISTICAL REVIEWER'S EVALUATION

Table 3R summarizes the reasonable worst case analysis based on the medical review team's assessment. The % of escapes were similar in the VPA arms for both Studies (60% for Study 30 and 67% for Study 31). The % of escapes were similar in the LTG arms for both Studies (48% in Study 30 and 53% in Study 31). The % of escapes was smaller in the LTG arm

Table 3R. Results of the reasonable worst case escape analysis*

Study	Analysis	LTG		VPA		p-value (unadj)
		n	# escape(%)	n	# escape(%)	
Study 030	ITT/reasonable WC	31	15 (48%)	35	21 (60%)	.344
Study 031	ITT/reasonable WC	45	24 (53%)	45	30 (67%)	.197
Combined	ITT/reasonable WC	76	39 (51%)	80	51 (64%)	.140
Stratified by Study	ITT/reasonable WC					.113

* An escape is defined as a patient who meets one of the "escape" criteria once the AED taper has been initiated. A patient who withdraws for a non-AE related reasons in LTG arm is considered as an escape for reasonable WC analysis.

(51%) compared to the VPA arm (64%). However, the difference did not reach statistical significance for either the combined ($p=.140$) or stratified analyses ($p=.113$).

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SWANG/827-1517/Draft: December 19, 1997, 1997/LAM_EF.ADD

This document consists of 4 pages of text (2 tables from this reviewer, 1 table from joint review of medical reviewer and this reviewer), 1 appendix, with a total of 5 pages.

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APPENDIX (From original statistical review and evaluation dated Dec. 2, 1997)

Table. Results of the analysis of efficacy data by Study

Study	Analysis	LTG		VPA		p-value (adj. for region)	p-value (adj. for center)	p-value (unadjusted)
		n	# completer(%)	n	# completer(%)			
Study 030	Per Protocol	22	11 (50%)	28	7 (25%)	.090	.391	.068
	ITT	31	11 (35%)	35	7 (20%)	.179	.504	.159
	ITT/WC	31	11 (35%)	35	14(40%)	.688	.459	.706
Study 031	Per Protocol	28	17 (61%)	36	6 (17%)	.000	.000	.001
	ITT	45	17 (38%)	45	6 (13%)	.002	.002	.008
	ITT/WC	45	17 (38%)	45	15 (33%)	.487	.281	.660
Combined	Per Protocol	50	28 (56%)	64	13 (20%)	.000	.001	<.001
	ITT	76	28 (37%)	80	13 (16%)	.003	.007	.004
	ITT/WC	76	28 (37%)	80	29 (36%)	.890	.752	.939

The sponsor's defined primary efficacy analysis

A completer is defined as a patient who completes 12 weeks of monotherapy treatment.

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