Memorandum

NDA: 22115
Sponsor: GSK
Name of Drug: Lamictal XR
Indication: Adjunctive Therapy of Partial Seizures
Date of Document: July 10, 2008
Type of Submission: Complete Response
Statistical Reviewer: Tristan Massie, Ph.D.

Background
This complete response submission attempts to address the issue of an apparently lower treatment effect in the U.S. as compared to the group of non-U.S countries in study LAM100034. The application relied on this single study and some problems with primary efficacy data were identified during an inspection of a particular foreign site. Therefore, the FDA Division of Neurology indicated that the sponsor needed to investigate the possible causes of the apparently lower treatment effect in the U.S. and address the inspection issues before the application could be approved.

The LAM100034 study investigated two groups (Lamictal XR versus placebo) as adjunctive therapy for partial seizures. The target Lamictal XR dose ranged from 200 to 500 mg/day depending on the identities of the pre-existing (1 or 2) stable AEDs. The study design involved an 8 week baseline period, 4 weeks of which were permitted to be retrospectively collected as determined by the sponsor on a case by case basis. The rest of the baseline period seizure data was prospectively collected. This was followed by the 19 week double blind phase: a 7 week titration phase followed by a 12 week maintenance phase. The primary efficacy measure was the percent change from baseline in the frequency of all partial seizures during the 19 week double blind treatment phase. The prespecified primary analysis called for comparing this between the groups using a Wilcoxon rank sum test and the treatment difference was to be estimated using the Hodge-Lehmann estimation method. Of the 243 randomized patients 36% (n=87) were entered in the U.S. Overall, ignoring any effects of country, the estimated treatment difference in the percent change from baseline in the frequency of all partial seizures was 18 percent between Lamictal XR and placebo, p=0.0004. In the U.S. the treatment difference was estimated to be just 3.5 **(**95% C.I.= -11.3 to 19.2**)** as compared to the estimate of 26.2 (95% C.I.=13.9 to 38.4**)** in the group of non-U.S. countries. A rank based analysis of covariance of the percent changes suggested that this difference in treatment effects between the U.S. and non-U.S. was nominally significant with a p-value of 0.03.

Key Content in the Complete Response Submission
The sponsor now believes (as suggested by the complete response submission) that the observed differences between the U.S. and non-U.S. may be due to an imbalance between the regions in the use of Valproate (VPA) as a concomitant AED. In particular, 4/42 (10%) U.S. subjects assigned to Lamictal XR were taking concomitant VPA while 26/74 (35%) non-U.S. subjects were doing so. They argue that if indeed VPA subjects respond earlier than non-VPA subjects, then this could explain why there was a better response in non-U.S. sites during escalation and subsequently, the entire treatment period. They also point to the higher placebo response in the U.S. (median percent change of 28.9 in U.S. versus 21.5 outside

U.S.) as another possible explanation for the apparent difference in treatment effects between the U.S. and non-U.S. However, it is not possible to resolve beyond a doubt the issue of a low treatment effect in the U.S. as compared to non-U.S. in study LAM100034. The sponsor's preferred explanations for this difference were identified post-hoc. Therefore, we must consider that many different possible explanations were investigated. We must then acknowledge that one of them may exhibit the desired correlation with the low treatment effect in the U.S. due to chance alone rather than due to a true causal relationship.

In particular, they also investigated the following other possible explanations for the differences between the U.S. and non-U.S. results but these investigations did not lead to any conclusive findings:

- Differences in Lamictal XR Exposure
- Differences in medical refractoriness to treatment
- Differences in use of old vs. new AEDs
- Differences in baseline seizure frequency
- Differences in demography
- Differences in LTG average maintenance doses
- Differences in days on treatment and premature discontinuation rates
- Differences in partial seizure type

There may be other differences between U.S. and non-U.S. sites that they did not investigate such as in the use of historical baseline (34% non-U.S. vs. 24% in U.S.). Although there is a slight difference between the U.S. and non-U.S. in the proportions that used historical baseline the differences in treatment effects between the U.S. and non-U.S. are reasonably consistent regardless of historical baseline use.

Sponsor's Conclusions

- Any difference in the efficacy of LTG-XR in U.S. and non-U.S. subjects is unlikely to be as a consequence of differences in pharmacokinetics and resulting serum concentrations observed in the two groups.
- There was an imbalance in the use of concomitant VPA between U.S. and non-U.S. sites with 87% of the VPA use occurring at non-U.S. sites, which is consistent with known regional differences in treatment of partial seizures.

- Concomitant VPA use together with a seven-week escalation phase appears to facilitate an earlier response to treatment with LTG-XR in combination with VPA which also contributes to a better response over the entire treatment period.

- In spite of the disproportionate contribution of VPA to the non-U.S. response, the response to treatment was statistically significant in both regions during the maintenance phase.

Reviewer's Note: Based on the data in the original submission of this NDA supplement the p-value for the treatment group comparison in the U.S. in the subgroup of patients with data during the maintenance period was p=0.08. The original data has now been revised according to the results of subsequent site inspections and the new p-value is 0.03 (median percent reductions: 58.3 Lam, 33.3 Pl). This maintenance period subgroup excludes 5 Lamictal XR patients that did not have any data for the maintenance period. If these patients (4 of 5 of whom had increases in seizure frequency during titration) are included using the available data during the titration period then the p-value becomes p=0.19 (median percent reductions: 50.4 Lam, 33.3 Pl).

- These effects of VPA are similar to those observed in previously conducted trials with LTG.

- For non VPA subjects, the median seizure reduction in the maintenance phase is similar, reaching statistical significance for the non-U.S. sites with a trend in the U.S. sites, possibly related to a higher placebo response in the U.S.

Reviewer's Comments

The primary analysis is reproduced in Table 1 below along with the results in the U.S. and non-U.S. subgroups. A test for a difference in treatment effect between the U.S. and non-U.S. based on a rank Analysis of Covariance was significant at the nominal level (p=0.03). The estimated treatment difference was 3.5 in the U.S. (N=84) as compared to 26.2 for non-U.S. countries pooled (N=152).

Table 1 Percent Change in Weekly Seizure Rate (mITT)

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	Median of Differences	Wilcoxon p
Country												
United States	42	2.4	32.8	24.3	51.0	42	2.6	37.1	27.0	49.8	3.49	0.340
All Non-U.S.	78	2.0	22.8	17.3	43.5	74	2.2	49.6	39.3	50.8	26.19	<0.001
All	120	2.1	24.2	19.7	46.2	116	2.3	46.1	34.8	50.6	18.17	<0.001

The following tables examine the treatment effects in the U.S. and non-U.S. over the entire treatment period in subgroups defined by the type of concomitant AEDs the patients were taking. The AED subgroups were defined by the sponsor as 1) Enzyme Inducing AEDs (EIAEDs) alone or with non-inducing/inhibiting AEDs, 2) VPA/DVS alone or with non-EIAEDs, 3) VPA/DVS with EIAEDS, or 4) Other Regimens.

Table 2 Percent Change in Weekly Seizure Rate, AED Type=EIAEDs alone or with non-inducing/inhibiting AEDs

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	Median of Differences	Wilcoxon p
Country												
United States	16	2.6	36.4	34.2	28.8	24	2.4	44.9	31.0	55.7	3.48	0.375
All Non-U.S.	27	1.8	15.8	17.3	36.7	35	2.5	40.7	35.1	33.6	18.54	0.027
All	43	2.0	25.6	23.6	34.6	59	2.5	42.1	33.4	43.5	11.70	0.040

Table 3 Percent Change in Weekly Seizure Rate, AED Type=All other regimens

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Change	Median of Differences	Wilcoxon p
Country												
United States	16	3.4	34.7	14.6	75.3	14	2.9	35.9	24.5	40.3	-1.25	0.492
All Non-U.S.	18	2.0	10.7	7.6	68.1	13	1.5	50.9	29.8	65.6	27.07	0.104
All	34	3.1	17.8	10.9	70.6	27	1.9	36.8	27.1	53.0	14.68	0.130

There were only 8 patients in the U.S. whose concomitant AEDs were categorized as VPA/DVS alone or with non-EIAEDs and only 6 categorized as VPA/DVS with EIAEDS. Therefore, there isn't much reliable data to elucidate differences in treatment effects between the U.S. and non-U.S. in these subgroups. Nevertheless, Table 4 shows results when these two AED categories are combined and while this reviewer acknowledges the limited usefulness of these analyses due to the small sample size in the U.S. they, like the other analyses, suggest a lower treatment effect in the U.S.

Table 4 Percent Change in Weekly Seizure Rate, AED Type=Any VPA/DVS

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Change	Mean Change	StdDev Change	N	Baseline Median	Median Change	Mean Change	StdDev Change	Median of Differences	Wilcoxon p
country												
United States	10	2.0	18.0	23.8	26.4	4	11.3	18.5	12.1	50.8	-7.52	0.416
All Non-U.S.	33	2.3	25.9	22.5	30.2	26	1.9	68.4	49.6	61.3	39.64	<0.001
All	43	2.1	24.2	22.8	29.1	30	2.1	60.3	44.6	60.6	34.19	<0.001

Table 5 Percent Change in Weekly Seizure Rate **excluding** AED Type=VPA/DVS alone or with non-EIAEDs

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	Median of Differences	Wilcoxon p
Country												
United States	37	2.4	33.3	23.3	53.4	39	2.4	37.4	28.0	49.5	3.89	0.324
All Non-U.S.	64	1.9	15.8	15.3	46.3	54	2.2	48.0	37.2	42.6	23.03	0.001
All	101	2.0	22.2	18.2	48.9	93	2.3	43.9	33.4	45.6	15.71	0.002

Table 6 Percent Change in Weekly Seizure Rate **Excluding** All VPA related AED categories

	Randomized Treatment Group											
	Placebo					Lamictal XR						
	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	N	Baseline Median	Median Pct Change	Mean Pct Change	StdDev Pct Change	Median of Differences	Wilcoxon p
Country												
United States	32	3.3	35.5	24.4	57.0	38	2.5	39.7	28.6	50.1	2.52	0.389
All Non-U.S.	45	1.8	12.3	13.4	51.1	48	2.3	41.4	33.7	43.8	20.80	0.006
All	77	2.0	24.2	18.0	53.5	86	2.4	41.4	31.4	46.5	13.10	0.014

In all of the concomitant AED subgroups considered the treatment effect was larger in the pool of non-U.S. sites than in the pool of U.S. sites. While the median percent reduction in seizure frequency for placebo was typically higher in the U.S. in these subgroups, i.e., there was a higher placebo effect, the median percent reduction for Lamictal was also lower in the U.S. than non-U.S. in several cases. It is not clear to this reviewer from the clinical data that the regional difference in treatment effects is due to the regional difference in VPA use. In conclusion, the lower efficacy in the U.S. was fairly consistent across the concomitant AED subgroups and while it may be possible to generate hypotheses for the underlying cause of the observed regional difference it is not possible to conclusively establish a causal relationship on the basis of the existing data. It is also important to keep in mind that there are many well known limitations of subgroup analyses that must be considered when evaluating subgroup analyses.

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