

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	Norman Hershkowitz MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22416
Supplement#	
Applicant	Sepracor Inc.
Date of Submission	2/10/03 (received 2/10/13)
PDUFA Goal Date	11/8/13
Type of Submission	NME, response to CR
Proprietary Name / Established (USAN) names	Aptiom / Esclicarbazepine Acetate
Dosage forms / Strength	200, 400, 600 and 800 mg
Proposed Indication(s)	Partial Onset Seizures
Recommended:	Approval

Cross Discipline Team Leader Review Template

1. Introduction

Eslicarbazepine acetate (ESL) is a dibenz[b,f]azepine compound, the chemical family of which also includes the anticonvulsants carbamazepine and oxcarbazepine. All such agents block the voltage-gated sodium channel (and perhaps calcium gated channels), which is believed to mediate their anticonvulsant action. Many anticonvulsants (e.g. phenytoin and lamotrigine) are believed to act through a similar mechanism. ESL exhibits not only functional but close structural similarities to oxcarbazepine. ESL may be considered a pro-drug. Thus, it is rapidly and almost completely metabolized to S-licarbazepine (eslicarbazepine); small proportions of R-licarbazepine and oxcarbazepine are also produced. Both S-licarbazepine and R-licarbazepine are thought to possess the predominant “sodium channel blocking” anticonvulsant activity of this compound in humans. Oxcarbazepine produces the same active metabolites, but in different proportions. The proportion of S-licarbazepine to R-licarbazepine, following oral administration of eslicarbazepine acetate, is 21:1, whereas the proportion following oxcarbazepine oral administration is 4:1.

The present response to a CR action is for the approval of ESL in the adjunctive treatment in partial onset seizures (POS). Well over 11 agents are presently marketed for the same indication. This includes those that are structurally and mechanistically similar (oxcarbazepine and carbamazepine), as well as a number of other agents with similar presumed mechanisms (e.g. phenytoin and lamotrigine), and others with potentially different mechanisms (valproic acid, gabapentin, vigabatrin).

2. Background

Eslicarbazepine acetate was developed by Bial-Portela & Ca.S.A. Sepracor is the U.S. sponsor of eslicarbazepine and the sponsor of this NDA. Development of this drug started in the year 2000 and mostly occurred outside and prior to the establishment of an FDA IND. The phase 3 clinical drug development program was wholly outside the United States. Two pre-NDA meetings occurred, one with Bial and another with Sepracor. One of the crucial issues discussed at these meetings was the absence of US data. The Sponsor was requested to provide an adequate justification for the exclusive use of non-US data in their NDA application.

ESL was given a favorable EMEA review approximately one and half years ago and is to be marketed in Europe under the brand name of Zebinix.

This application was initially submitted on 3/30/09, but received a CR response on 4-30-10. The basis for the CR response was that of significant and serious deficiencies related to the conduct and documentation of the studies that were revealed through site inspections and

application review. The letter made a number of requests, which are described in Section 11 of this review, under “Data Integrity” issues. The potential need for additional studies was expressed in the letter. A number of meetings and communications subsequently occurred, many of these to specifically define what will be required in a response to the CR. These are discussed in this review. A response to CR was finally received on 9-4-12. This response included the addition of an additional safety/efficacy trial as well as third party audit reports on almost all sites. This submission, however, was designated as incomplete because of continuing inadequacies in data presentation and completeness in the application. The application was finally received on 2/10/13 and was filed. A latter three month extension was given because of the degree of additional data and analyses that were requested.

3. CMC/Device

Following the first round of review, CMC noted that the application should be approved as the drug substance was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, physical properties and consistency in manufacture and that the manufacturing process for the drug product was adequately studied and that the drug was produced in a controlled and consistent fashion. All production sites were inspected and reviewed and given an “acceptable decision.” The CMC reviewer for the present response is Dr. Jewell. He did not note any new problems except those identified by Biopharmaceuticals that are described below.

Dr. Angelica Dorantes performed the biopharmaceutical review. Off note, the Sponsor intended in their original NDA to manufacture three dosages strengths (400 mg, 600 mg and 800 mg) (b) (4)

(b) (4) the agency requested that (b) (4) a new 200 tablet strength be introduced, for titrations in patient with moderate to severe renal failure (see section 5 Clinical Pharmacology /Biopharmaceutics). The Sponsor has done so and has now provided dissolution data to justify a biowaiver for the new 200 mg tablet. Dissolution data is provided as follow:

(b) (4)



The dissolution of the 200 mg was observed (b) (4) and a biowaiver was therefore initially rejected by the reviewer. A PK study was recommended by that reviewer. It might be argued that a biowaiver is unnecessary as this is only indicated for the renal titration period, but I would like to point out that once marketed it will be assumed that multiple 200 mg tablets are equivalent and interchangeable with

equivalent dosage higher strength tablets. As a result, the lack of bioequivalence does not only apply to short term usage. The Sponsor was informed of this action and has provided new data and requested a reconsideration of this decision. The new information convincingly demonstrated to the Biopharmaceutical reviewer that the present 200 mg strength would be bioequivalent. This was based upon the demonstration that different 200 mg strength tablet was bioequivalent. (b) (4)

One other issue raised by the biopharmaceutical reviewer raised was that of the (b) (4) method used in clinical one of the clinical trials. While, based upon the reviewer's table, a number dosage strengths appear similar dissolutions (b) (4) of two 400 mg tablets to produce appear to have (b) (4) by about 30 minutes. This was discussed in the Division at a group meeting, and it decided that this (b) (4) should not affect the applicability of the study to labeling of the final product. Later inquiries by the medical reviewer, Dr. Podruchny, determined that the study using this (b) (4) product was an abuse study, and therefore would have no impact on efficacy conclusions.

4. Nonclinical Pharmacology/Toxicology

Dr. Toscano, Pharm/Tox reviewer, performed the initial and present non-clinical review. In his first review Dr. Toscano noted that, with the exception of one deficiency, the application contained an adequate non-clinical assessment of the pharmacology and toxicology of ESL. Thus, although a single long term mouse carcinogenicity study was performed (demonstrating hepatic tumors after 2-years), it was concluded that there was inadequate *in vitro* data exploring carcinogenicity potential for this agent. The Sponsor was requested to conduct an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing), testing eslicarbazepine directly with and without an appropriate metabolic activation system (metabolic pathway for ESL in humans and rodents are very different). Nonetheless, the final conclusion of Dr. Toscano's first review concluded that ESL's overall nonclinical profile is similar to that of other approved anticonvulsants and should be approved with appropriate labeling. The *in vitro* studies were submitted in this submission and Dr. Toscano noted that studies for ESL in the presence or absence of human S9 fraction in the *in vitro* bacterial reverse mutation assay and the *in vitro* chromosomal aberration assay in human peripheral lymphocytes were negative. These studies were believed to be adequate.

Dr Tosacno, believes that based upon this new and prior data that the application can be approved. Although not requested, or required, for a response to the CR, the Sponsor submitted Beagle Juvenile studies. The studies demonstrated mortality at all doses in the pivotal trial studied (40, 80, 160 mg/kg) in the pivotal study. Bone marrow and lymphoid tissue depletion was observed. Convulsions were observed in juvenile animals dosed with 160 mg/kg eslicarbazepine acetate. Because of lack of the identification of a NOAEL, additional

animal studies will be required before pediatric studies are attempted. Dr. Toscano recommends the placement of these juvenile animal findings in section 8.4 of the label. Dr. Freed, Pharm/Tox team leader, notes that the interpretation of the juvenile study is complicated by some technical aspects of its execution including the selection of lower body weights animals for analysis. Nonetheless, she agrees that an additional juvenile animal study would be needed to determine safe starting doses in pediatric patients; she also notes the need for enhanced monitoring of pediatric patients during clinical development. She notes the study should be “focused on further characterizing the potential immunotoxicity of eslicarbazepine acetate.” She also opines that this should be a Postmarketing Requirement as part of PREA.

Dr. Freed also comments on case report examining Oxcarbazepine in human milk as well as animal studies examining the same, and notes problematic technical issues that obfuscate any interpretation.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Veneeta Tandon and Kofi Kumi performed the first Clinical Pharmacology review. Both concurred that the PK studies were adequate and the application should be approved. Only one non-obligatory recommendation was made in the first review, which was to develop a 200 mg dosing strength. The principal points raised in the first review are described below, along with the new issues raised in this submission. Dr. Yu performed the OCP review of the present response to the Complete Response.

The to-be marketed formulation and the formulation used in the pivotal clinical trials were considered bioequivalent. Dosage strengths were determined to be equivalent. The DSI inspection results were acceptable. No food effect was apparent.

As noted above, oral ESL can be considered a prodrug to S-licarbazepine, which represents 95% of the circulating species, and is believed to exert its predominate anticonvulsant action. Metabolism is believed to occur by hydrolytic first-pass metabolism in the presence of hydrolase; other active metabolites are produced in substantially smaller amounts and include R-licarbazepine and oxcarbazepine. Additional inactive metabolites are produced and account for a small percentage of that circulating (3%). Bioavailability is high. Tmax of S-licarbazepine occurs in about 1-4 hours. Protein binding is relatively low (<40%).

ESL metabolites (including its principal active metabolite, S-licarbazepine) are predominately eliminated by the kidney, mostly in the form of free S-licarbazepine (approximately two-thirds) and conjugated S-licarbazepine (one third). The T1/2 in epilepsy patients is 13 to 20 hours.

Pharmacokinetic studies indicated dose proportionality in the range of 400 to 1200 mg/day, doses equivalent to Sponsor recommended labeled dose (400 to 1200 mg/day).

The initial clinical pharmacology review noted that the extent of systemic exposure ($AUC_{0-\infty}$) to S-licarbazepine was increased by 62%, 116%, and 154% in the mild, moderate, and severe renal impairment group, respectively. (b) (4)

[Redacted]

[Redacted] (b) (4)

(b) (4) it was recommended that the Sponsor develop a 200 mg dosage strength for QD dosing, as such dosing would result in greater superimposability of dosing curves and may be easier to administer. It should be noted that while there is a small pharmacokinetic advantage, there is no hard evidence to indicate that this regimen would be advantageous from a therapeutic point of view. (b) (4)

[Redacted] This request was therefore not mandatory. The Sponsor developed the 200 mg strength, which was submitted in the response to a Complete Response. The agency will therefore be approving the 200 mg strength, which can be used for titration in cases of moderate to severe renal failure. (b) (4)

[Redacted]

Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine and dosage adjustment is not necessary.

No significant change in the pharmacokinetics was apparent in the elderly with creatinine clearance > 60 mL/min. Children were not studied.

The first review noted that that Eslicarbazepine is an inhibitor of CYP2C19. Significant reduction in levels of oral contraceptives and warfarin was noted that will require cautionary labeling. With regard to its effect on other anticonvulsants, while all were not studied, the only significant interaction was an increase in phenytoin exposures, which may require a reduced phenytoin dose. Also noted is observation that phenytoin, carbamazepine and phenobarbital may reduce ESL exposure, requiring an increased ESL dose (see also Section 7, Clinical/Statistical-Efficacy).

Additional specific information on interactions have been submitted in this response to the CR action that include the following drug-drug interaction information : 1) specific information on CBZ interaction that demonstrate that the AUC and Cmax of eslicarbazepine decreased by 32% and 22% following the concomitant administration with CBZ, for which a higher dose of ESL is being recommended in the label, 2) specific information on reduction in levonorgestrel and ethinyloestradiol following ESL treatment, which require additional labeling recommendations, 3) information on the decrease in some statins following treatment of ESL, which will require labeling recommendations. A study comparing CSF and blood concentration fluctuations for ESL and oxcarbazepine was included in this submission. This study demonstrated that CSF concentration fluctuation of the active drug is less than blood concentration fluctuation. (b) (4)

Metabolism did not appear to be significantly affected by race (black versus Caucasian) or sex.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Three pivotal Phase 3 efficacy/safety studies will be used to determine the efficacy of ESL; these include study 301, 302 and 304. Two of these studies (study 301 and 302) were previously reviewed by the clinical and statistical teams Dr. Podruchny and Dr. Ling, respectively; a discussion of studies 301 and 302 are included in this CDTLs previous review. A new study (study 304) has been submitted, which is largely the subject of the present review. This study has also been reviewed by Dr. Podruchny and Dr. Ling. The older studies will first be discussed.

Studies 301 and 302

Although 3 randomized, placebo-controlled, and multi-center trials (studies 301, 302 and 303) were reviewed in the first cycle to serve as pivotal trials to support adjunctive treatment in partial onset epilepsy, only two of these (studies 301 and 302) were submitted by the Sponsor to support efficacy because of data integrity issues in the third study. Study 303 was to be considered as supportive. Because of this, studies 301 and 302 were the principal studies reviewed as part of the initial NDA review. Dr. Ling performed a brief follow-up review on these studies as a result of additional information received in the response to the CR (see below).

These studies were wholly performed outside the US, in locations that included Eastern Europe, Western Europe, Latin America, Australia and South Africa.

Studies 301 and 302 were of relatively typical design for studies that examine adjunctive treatment of epilepsy. Patients were recruited and entered into an 8-week placebo period. Only subjects who fulfilled minimal frequency requirements during the baseline period were randomized to one of four treatment groups (placebo or ESL 400mg, 800mg or 1200mg qd); these patients subsequently entered the treatment phase of the study. The treatment phase consisted of a 2 week titration period followed by a 12 week maintenance period.

It is noteworthy that an important exclusionary criterion in these studies was that patients should not be on oxcarbazepine, a drug that shares the same active metabolite as eslicarbazepine.

The source of data were event diaries, which record a seizure only if it occurs on a particular day, and does not require the obligatory recording of the absence of seizures on days when none occur. The primary endpoint was absolute logarithmically transformed seizure frequency¹ during maintenance, which was compared among the treatment groups by using an analysis of covariance (ANCOVA) that models seizure frequency as a function of baseline seizure frequency and treatment. Only patients who entered the maintenance phase were analyzed. Because it is more common to include, as a modified intent to treat set, all randomized patients with at least one administration of study medication and at least one post-baseline seizure frequency assessment, which would include titration data, the statistician performed sensitivity analyses. Dunnett's multiple comparison procedure was used for the comparison of each active treatment group to the placebo group and corrected for multiple comparisons. All p values for the primary endpoint are presented so that they are adjusted for multiplicity (statistical significance criteria of $p < 0.05$).

¹ Natural logarithm transformation was carried out according to the following formula: $\text{Ln}(\text{standardized seizure frequency} + 4)$. The standardized seizure frequency for a period was calculated as: $(\text{number of seizures/days in the period} * 28)$. The logarithmic transformation is performed to normalize the data.

Study 301

No obvious demographic or baseline differences were apparent across treatment groups. All patients were categorized as Caucasian. Data and analyses (from the statistical review) for the primary endpoint are presented in the table below.

Study 301: Seizure Frequency per 4 Weeks over the Maintenance Period (Sponsor updated result)

	Placebo	Eslicarbazepine Acetate Dose Group		
		400 mg	800 mg	1200 mg
N	99	97	93	92
LSmean (SE)	7.5 (0.67)	6.7 (0.60)	5.6 (0.58)	5.4 (0.56)
95% CI	6.3, 8.9	5.6, 8.0	4.6, 6.9	4.4, 6.6
Log Difference in LSMean (SE)		-0.07 (0.055)	-0.18 (0.055)	-0.20 (0.056)
95% CI for Difference in LSMean		-0.20, 0.06	-0.31, -0.05	-0.33, -0.07
p-value		0.4067	0.0041	0.0009

Source: Sponsor's response to October 8, 2009 Request for information and is confirmed by FDA reviewer. Without imputation, baseline AED as covariate

Only the 800 mg/day and 1200 mg/day group were determined to be statistically significantly different from placebo. Of note the LSmean change represents the absolute difference in seizures frequency (transformed back from logarithmic transformed endpoint) and is in terms of seizures per month. The median percent reductions in seizure frequency from baseline to maintenance over placebo, which I believe is more easily interpreted, was in these two groups, based upon the Sponsor's calculation, 16.5% and 18.1% for ESL 800mg/day and 1200mg/day, respectively.

The Sponsor concludes that doses of 800 and 1200 mg/day produced statistically significant effects. Similar results were observed in the Sponsor's analysis of 50% responder rates, a secondary endpoint, with only the 800 and 1200 mg/day dose producing a statistically significant effect (adjusted for multiple comparisons) as compared to placebo (ESL 1200 mg group of 44.6% and the ESL 800 mg group of 35.5% compared to the placebo group of 20.2%).

The statistics reviewer notes that the data provided by the Sponsor was "hardcoded" to correct for errors that were introduced in the original datasets. These hardcode corrected for these errors. The statistics reviewer examined this issue and determined that this hardcoding affected 559 data-points. Some of these hardcodes resulted from an unblinded review. Such problems were evenly distributed across treatment groups. A sensitivity analysis, with removal of the hardcodes, produced similar results as that observed with the hardcodes. While the statistics reviewer did not believe the degree of hardcoding affected the final conclusions she did believe that such a degree was unusual and that it reflected on the poor conduct of the study.

Another issue noted by the statistics reviewer is that while it is routine for patients to maintain record of seizures by updating a diary, which serves as the source of the primary endpoint calculation, subjects were instructed to update their diary only on days when they had seizures

(event diary). This meant that diary cards that were not filled out or returned were assumed to represent days without seizures. Moreover, the last diary returned was assumed to represent the last day in the trial and used to calculate the denominator for frequency. However a worst case scenario sensitivity evaluation was, according to the statistics reviewer, “still favorable.”²

Another issue considered by the statistician was the use of only patients who reached the maintenance phase. This, as noted above, is not a typical modified ITT analysis. The statistician performed a sensitivity analysis and found that this did not influence the final conclusion.

The statistics reviewer considered two additional issues in the Sponsor’s analysis of this study, including her observation that : 1) logarithmic transformation should have used a slightly different analytic manipulation, 2) the original SAP ANCOVA analysis identified only frequency and treatment as covariates, but the Sponsor added the “number of concomitant AEDs” as a third covariate. The FDA statistician recalculated data performing a correction for these factors and found similar statistical significance for the 800mg/day and 1200 mg/day doses.

The statistician also performed a calculation of the primary endpoint excluding site 112, which was determined to be problematic by inspection, and observed a similar statistical significance of the two highest doses.

Study 302

Demographic variables in this study tended to be well distributed over the treatment groups except for slightly fewer Caucasians in the 1200 mg/day treatment group and fewer males in the 400 mg/day treatment group. Baseline characteristics were similar except for a trend toward slightly lower baseline seizure frequency in the placebo groups (thus median baseline frequencies were 7.4, 8.2, 9.1, and 9.3 seizures per 4 weeks in the placebo and ESL 400 mg, 800 mg and 1200 mg groups, respectively). These differences, however, were small and the analysis statistically corrects for baseline.

The Sponsor’s statistical evaluation of the primary endpoint revealed that the dose groups of 800 and 1200 mg/day were statistically significantly different from the placebo group (see table below, from the statistical review). The treatment effect in the 400 mg/day dose group was not determined to be statistically significant. These calculations were confirmed by the FDA statistician. These data translate into median percent reductions in seizure frequency over placebo of 16.5% and 13.9 % for the 800 mg/day and 1200 mg/day groups, respectively. A worse case scenario analysis³ to correct for the patient diary reporting problem (see study 301) was still “favorable” to an effect. The 50% responder rate exhibited a similar result as the primary endpoint evaluation.

² The worst case scenario calculation revealed a p-value of 0.0599 for the 800 mg group and from 0.0009 for the 1200 mg group.

³ The worst case scenario calculation revealed a p-value of 0.031 for the 800 mg/day group and 0.078 for the 1200 mg/day group.

	Placebo	Eslicarbazepine Acetate Dose Group		
		400 mg	800 mg	1200 mg
N	99	94	87	81
LSmean (SE)	10.0 (0.67)	9.2 (0.65)	7.6 (0.59)	8.0 (0.62)
95% CI	8.7, 11.3	7.9, 10.5	6.5, 8.8	6.8, 9.2
Log Difference in LSMean (SE)		-0.06 (0.061)	-0.18 (0.062)	-0.15 (0.063)
95% CI for Difference in LSMean		-0.20, 0.08	-0.33, -0.04	-0.30, 0.00
p-value		0.6524	0.0095	0.0420

Similar to study 301, the statistics reviewer performed analyses adjusting the logarithmic formula, covariates, and use of only patients during maintenance to define an ITT population. These analyses indicated that the 800 mg/day group maintained its effect, but statistical significance was lost in the 1200 mg/day group. Hardcoding was not as much an issue in this study, as their use was more transparent. A sensitivity analysis, examining the affect of hardcoding, indicated that it did not influence the final conclusion of efficacy.

Study 303

As noted in this CDTL's original NDA review, the data in this study were considered suspect and are therefore not considered in the evaluation of efficacy. Study 303 was similar in design to those studies noted above, however study 303 examined only three experimental groups (placebo, 800 mg/day and 1200 mg/day) and was carried out mostly at sites in Mexico, with some in Spain and Portugal. Analysis revealed that both experimental drug groups exhibited a statistically significant reduction in seizures as compared to the placebo control group. The analysis was confirmed by the FDA statistician. A reanalysis of the data, which was updated to incorporate changes in deriving the efficacy variable resulted in statistical significance only in the 1200 mg/day group.

Subgroup analysis

As per the statistical reviewer, no obvious sex, age or racial factors appeared to influence the drugs effect. These data were limited, however, by small numbers of patients older than 60 years old and who was not Caucasian. The number of patients of both sexes was adequate.

Whereas the statistical reviewer did not perform an analysis of sub-categories of partial onset seizures by type (simple partial, complex partial and partial secondary generalized), the

Sponsor presents such an analysis in one of their tables in the integrated summary of efficacy, shown below. Only patients having a particular seizure subtype during baseline were analyzed, leaving the conclusions open to bias resulting from the loss of randomization and sampling error. Nonetheless, while the table indicates favorable trends (and even statistical significance) in two seizure subtypes (simple partial and complex partial seizures), no trend is indicated in the partial secondarily generalized seizures. However, as will be observed below, a trend was observed in study 304.

Table 3.4.2.1-5: Analysis of Relative Change in Standardized Seizure Frequency During the 12-Week Maintenance Period for the Pooled Pivotal Phase III Studies 2093-301 and 2093-302 by Seizure Type (Model 1, without Interaction) - ITT Analysis Set

Seizure Type	ANCOVA Statistic ^a	Placebo	Eslicarbazepine Acetate Dose Group		
			400 mg	800 mg	1200 mg
Simple Partial	N	92	85	86	85
	LS Mean (SE)	39.6 (13.41)	3.8 (13.86)	-22.2 (13.74)	-20.2 (14.21)
	95% CI	13.2, 66.0	-23.5, 31.1	-49.2, 4.8	-48.1, 7.7
	Diff in LS Mean (SE)		-35.8 (16.83)	-61.8 (16.68)	-59.8 (16.73)
	95% CI for Diff in LS Mean		-75.6, 4.0	-101.2, -22.4	-99.3, -20.3
	p-value ^a		0.0885	0.0007	0.0012
Complex Partial	N	144	137	131	137
	LS Mean (SE)	1.2 (8.23)	-20.6 (8.45)	-27.0 (8.81)	-23.4 (8.40)
	95% CI	-14.9, 17.4	-37.2, -4.1	-44.3, -9.7	-39.9, -6.8
	Diff in LS Mean (SE)		-21.9 (9.81)	-28.2 (9.87)	-24.6 (9.78)
	95% CI for Diff in LS Mean		-45.0, 1.3	-51.5, -4.9	-47.7, -1.5
	p-value ^a		0.0686	0.0124	0.0333
Partial Evolving to Secondarily Generalized	N	75	66	62	64
	LS Mean (SE)	-54.8 (24.08)	-9.2 (24.26)	-29.1 (25.57)	-55.0 (24.53)
	95% CI	-102.2, -7.3	-57.0, 38.6	-79.4, 21.3	-103.3, -6.7
	Diff in LS Mean (SE)		45.6 (28.20)	25.7 (28.62)	-0.2 (28.44)
	95% CI for Diff in LS Mean		-21.3, 112.4	-42.1, 93.5	-67.4, 67.1
	p-value ^a		0.2567	0.7052	>0.9999
Unclassified	N	24	19	22	21
	LS Mean (SE)	-65.2 (15.77)	-38.2 (18.15)	-52.5 (18.00)	-52.4 (17.28)
	95% CI	-96.6, -33.8	-74.3, -2.1	-88.3, -16.6	-86.8, -18.0
	Diff in LS Mean (SE)		27.0 (20.89)	12.7 (20.77)	12.8 (20.67)
	95% CI for Diff in LS Mean		-23.1, 77.1	-37.1, 62.5	-36.7, 62.4
	p-value ^a		0.4338	0.8748	0.8704

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Abbreviations: ANCOVA=analysis of covariance; LS=least squares; SE=standard error of the mean; CI=confidence interval; Diff=difference.

a ANCOVA model with fixed effects for treatment, study, baseline standardized seizure frequency, and number of concomitant AEDs at baseline, without the treatment by study interaction.

Summary of Effect

The statistics reviewer prepared the following summary tables from her analysis for all three studies (301, 302 and 303), which corrects for the ITT analysis (using titration data for patients without maintenance data). This includes the primary endpoint, 50% responder rate and percent reduction from baseline.

Primary endpoint: maintenance seizure frequency (LS mean)

		Placebo	Eslicarbazepine Acetate Dose Group		
			400 mg	800 mg	1200 mg
301	LSmean	6.9	6.2	5.2	4.8
	p-value		0.5136	0.0125	0.0007
302	LSmean	9.2	8.2	6.8	7.5
	p-value		0.5368	0.0072	0.1143
303	LSmean	6.8		5.3	5.0
	p-value			0.0887	0.0335

Secondary endpoint: 50% percent of responder during maintenance – responder/total (percent)

		Placebo	Eslicarbazepine Acetate Dose Group		
			400 mg	800 mg	1200 mg
301	n/N (%)a	20/102 (19.6)	23/ 98 (23.5)	34/ 98 (34.7)	42/ 97 (43.3)
	Chi-square p-value		0.6225	0.0249	0.0006
302	n/N (%)a	18/100 (18.0)	20/ 96 (20.8)	33/ 98 (33.7)	32/ 94 (34.0)
	Chi-square p-value		0.7483	0.0183	0.0169
303	n/N (%)a	21/ 84 (25.0)		29/ 84 (34.5)	34/ 77 (44.2)
	Chi-square p-value			0.2375	0.0167

Unadjusted p-value from pair wise test of each active treatment group compared to placebo.

Percent reduction from baseline

		Placebo	Eslicarbazepine Acetate Dose Group		
			400 mg	800 mg	1200 mg
301	LSmean	-7.7	-15.9	-28.4	-29.6
	p-value		0.6391	0.0373	0.0262
302	LSmean	3.6	-10.8	-17.9	-5.3
	p-value		0.2773	0.0521	0.6574
303	LSmean	-2.0		-19.3	-18.8
	p-value			0.3165	0.3522

Based upon the above the data the statistical reviewer concludes that the 800 mg/day dose is no better then the 1200 mg/day dose.

Additional Reanalysis of Studies 301 and 302 based upon the Present Response to CR

Dr. Ling performed a statistical analysis of studies 301 and 302 to address specific issues that she identified and that followed a nearly 100% audit. Included in this reanalysis was the

exclusion of two non-compliant sites, and redefinition of study periods. She notes that in Study 301, two sites were determined to have significant violations (Sites 174 and 175, constituting a total of 20 subjects). The audit finding also resulted in the addition of 115 seizures out of 22,538 in the total database, as per Dr. Podruchny. Moreover, Dr. Ling identified a potential consistent error in the calculation of seizure frequency. This error involved the fact that if a diary was missing on the last days, frequency calculations would assume such days has 0 seizures. She corrected for the former problem by excluding the two sites in question and the latter issue by ending frequency calculations at the last day of observed seizures. This did not change the observation of statistical significance for both the 800 and 1200 mg dose, although the p value was reduced. The trend of effect, on my observation of the data, is similar to that observed prior to correction, with subtle dose-response when moving from 800 mg to 1200 mg in study 301, but a relatively flat relationship in study 302. It should be noted that Dr. Ling concludes in her most updated analysis that "... Phase III studies 301 and 302 suggested marginal efficacy of ESL."

Conclusion

I agree with the original statistics reviewer that, at face, the data for the earlier studies indicates efficacy for doses of 800 mg/day with the 1200 mg/day dose offering no additional protection, on average, than the 800 mg/day dose. The effect size is similar to what I have seen for other anticonvulsants, albeit on the low side. Between both studies there was very little additional effect when comparing the 800 mg/day dose with that of 1200 mg/day. As will be seen in the safety section there is a substantial increase in adverse events at the higher dose. Two observations are noteworthy. The first is that the 800 mg/day dose failed to show a statistically significant effect in study 303. If, indeed, this study was performed in the absence of good GCP guidelines false negatives, would not be completely unexpected considering the increase variability introduced by the studies poor performance. Therefore, one must view such results as noncontributory. The other issue is the absence of a statistically significant effect when the true ITT population is evaluated in the 1200 mg/day group in study 302. This is likely a result of including patients who dropped out during titration but were still in the titration phase, thereby having low exposures. Supporting the effect at 1200 mg/day is the effect observed in the 1200 mg/day group in study 301 and the "supportive study" 303 as well as relatively consistent effects observed for 800 mg/day groups (with the exception of study 303). This is also supported by positive effects at 1200 mg in Study 304 (see below). Lastly, as noted above, there is some question as to whether partial secondarily generalized seizures are also suppressed by the medication, although such subgroup analyses should be interpreted with caution. Study 3, however indicates that such seizures are reduced by drug (see below).

While in sum these results suggest that ESL possesses anticonvulsant activity this conclusion can only be considered as tentative because the larger overarching issue of data integrity. The final conclusion is therefore dependent on study 304, which will be discussed below. Nonetheless, it should be pointed out that conclusions regarding efficacy may be less problematic than those of safety when GCP practice is not adhered to. That is sloppy studies would be expected to increase background noise (variability) which may make it more difficult to conclude a statistically significant effect. Nonetheless, efficacy was concluded from the data in the original statistical review. Two additional issues that may confound prior studies

included: 1) the use of event diary, 2) the fact that the studied population were derived from sites that were solely of non-US origin. For this reason the Sponsor was asked to conclude an ongoing study (study 304) and include that study in their response to CR. This response to CR is described below.

Study 304

As noted above, Dr. Ling and Dr. Podruchny of statistics and DNP, respectively, performed the review of this additional study.

The design for this trial was similar to that for studies 301 and 302 with some exceptions. Amendments in Study 304 allowed for a dose reduction of concomitant carbamazepine or phenytoin for intolerable adverse events during the maintenance phase. Additional pertinent amendments were made to this protocol so as to address FDA concerns regarding the interpretability of the data, which came about as a result of the first cycle of review of protocols 301 and 302 for this NDA. Thus: 1) because the original series of studies lacked patients from North American sites, an amendment was added to recruit North America patients (USA and Canada), 2) while the initial protocol called for event entry diaries, an amendment asked for daily entry diaries; to respond to this the Sponsor amended the protocol so that all new patients will use daily diaries; they also increased the sample size from 360 to 615 so as to be able to accrue sufficient patients to provide a 90% power for the subgroup using only daily diaries.

Also like those study 301 and 302 patients on oxcarbazepine were excluded from the randomization.

Patients were randomized (1:1:1) to one of three groups (ESL 800 mg QD, ESL 1200 mg QD or placebo). The primary endpoint was identical to the above studies, and secondary endpoints were similar. Analysis of the primary endpoint analysis was also similar to the above studies, using ANCOVA of logarithmically transformed data and the Dunnett's and Bonferroni's method to correct for multiple comparisons. All p values for the primary endpoint are presented so that they are adjusted for multiplicity (statistical significance criteria of $p < 0.05$). A total of 640 patients were included in the ITT population, with 185 patients using the event diary and 455 using the daily diary. Eighty-seven percent to 93% of patients in each arm entered the maintenance phase. Adverse events were the most common reason for discontinuation in all arms, including placebo, but discontinuation for adverse events were 4 times more likely in the high dose group than placebo. Demographic variables were generally well balanced between all treatment groups. Most subjects were classified as "whites" (approximately 63%), with the next common racial groups being Asian (approximately 20%). "Blacks" or "African Americans" made up about 3% of studied population.

Results for the primary analysis of the primary endpoint for the modified ITT as well as for the subgroup of patients who used daily diaries (DE ITT) are presented in the table below. The table is transcribed from the statistics review. Analysis for the primary set revealed statistical significance reduction in seizures only for the 1200 mg/dose group. Although, a reduction was

observed in the 800 mg/day group the p value missed the criteria for a statistically significant effect (0.059) by a small amount. These data translated into percent reductions in seizure frequency over placebo baseline revealed 16.3% and 22.9% change for ESL 800mg and 1200mg groups, respectively.

	Placebo	ESL 800 mg	ESL 1200 mg
Modified ITT population			
N a	212	200	184
LS mean (SE)	7.88 (0.49)	6.54 (0.41)	6.00 (0.40)
95% CI	[6.98, 8.90]	[5.77, 7.40]	[5.26, 6.84]
Log difference in LS mean		-0.18	-0.26
Unadjusted p-value		0.029	0.002
Adjusted p-value b		0.058	0.004
DE ITT population			
N a	154	137	136
LS mean (SE)	7.54 (0.54)	6.32 (0.48)	5.96 (0.46)
95% CI	[6.55, 8.68]	[5.44, 7.35]	[5.12, 6.94]
Log difference in LS mean		-0.17	-0.22
Unadjusted p-value		0.094	0.026
Adjusted p-value c		0.167	0.049

a Subjects who discontinued from the study during the titration period were not included.

b Bonferroni's procedure was used to calculate the p- values.

c Dunnett's procedure was used to calculate the p-values (assessed at 0.025 level). Source: Table 19 & 20 of the CSR for Study 304, confirmed by the reviewer.

A sensitivity analysis, using a non-parametric ANCOVA, by the statistical reviewer on the ITT population was consistent with the primary analysis with an unadjusted p-value 0.038 for the ESL800 mg group and 0.006 for the ESL1200 mg group.

As noted above the analysis set was only those patients who entered the maintenance phase. Typically this cannot be considered a true ITT like sample (patients who drop out during the 2 weeks of titration are not included). Both the Sponsor and statistical reviewer performed a number sensitivity analyses to explore this issue. All of these revealed results similar to the primary endpoint conclusions. One such analysis was to analyze the set that is usually used; i.e. all patients who entering the titration phase, who received at least one dose of drug, and had one primary endpoint determination (last observation carried forward). This is presented in the table below.

	Placebo N=220	ESL 800 mg N=215	ESL 1200 mg N=205
Combined Titration and Maintenance Period			
LS mean (SE)	8.68 (0.52)	6.60 (0.40)	6.31 (0.39)

Log difference in LS mean		-0.26	-0.31
Unadjusted p-value		0.001	<0.001

As noted above, two important changes were made to the protocol in the form of amendments, the addition of North American patients and the use of event diary. Thus in the final tally for the protocol, 212 patients were recruited in North America as compared to 385 patients from the rest of the world. One-hundred and sixty five patients used the event diaries and 428 used the daily diary. Dr. Ling notes that there were no statistically significant interactions between treatment and diary version, or between treatment and region (0.10 level). But, there was a trend for the event diary to be associated with a greater effect in the large subgroup of “Rest of the World”, which excludes North American subjects. Dr Ling explored issues surrounding daily and event diaries, which was an issue that may potentially confound studies 301 and 302. She described a number of potential factors which may confound data in event diaries (e.g. the assumption of no seizures if the diary is missing, errors in transcription, defining the end of the observation period defined by the last date of diary return) and concluded, based upon her exploration in study 304, the following:

“Based on the review of the dataset and select CRFs, the problems noted above were not deemed common. There could be other problems that we have not identified yet. It is not sure if collectively they could undermine the credibility of EE diary. However, the evidence to date may not be enough to dismiss EE diary data entirely, although some sort of discounting of the EE diary data may be reasonable.”

An analysis of the daily diary alone still revealed a statistically significant effect at the high dose and trended at the lower dose. Trending was noted for the event diary as well, but there was no mention in the review of statistical testing in that group, which may be underpowered for such an evaluation. Although, I think any definitive conclusions regarding differences between these two methods of collecting data is difficult, in this CDTL’s opinion, this analysis suggests that while the daily diary are superior to the event diary, analysis of the event diary should not be excluded in the interpretation of the effect of ESL. Dr. Podruchny feels stronger regarding the need to discount the event diary based upon her reading of Dr. Ling’s review. Perhaps the basis of this is based upon Dr. Ling’s statement, “problems that we have not identified yet” (see above quote for context). It seems to this reviewer that in general Dr. Ling believes that potential errors were not observed to a large degree, based upon the analysis of Study 304, and while one can look at the data obtained from event diaries with some degree of question, one cannot entirely dismiss it. The two studies using only the event diaries observed similar results as the present subgroup analysis using the daily diary. Lastly, as I see it, it might be expected that errors resulting from the event diary should be equally distributed across all groups, or, at least, it has not been explained how such errors could be biased toward one or another group. I believe that based upon Dr. Ling’s findings that studies 301 and 302 can contribute to our decision of drug efficacy. Indeed in her final conclusions Dr. Ling notes “The data overall provided evidence to support for the efficacy of Eslicarbazepine acetate as adjunctive treatment in patients with partial-onset seizure.”

Dr Ling discussed secondary endpoints of the 50% responder rates and the percent change in seizure frequency, both of which revealed similar results to the primary endpoint.

Analyses of covariates for the primary endpoint were performed. No significant effects were observed for age group, region or race. Sex, baseline carbamazepine use, baseline lamotrigine use, and baseline valproic acid use were thought to be significant covariates. Dr Ling notes a slightly greater effect in males, but my perusal of the data does not reveal this to be large in magnitude. Dr Ling notes that the effects were somewhat smaller in North America than the rest of the world

As noted above, I was concerned with the general lack of effect on partial secondary generalized seizures when data were sub-grouped by seizure type. In her review Dr. Podruchny presents the Sponsor's table of seizures by subtype, which is transcribed below. In those prior studies, consistent with my description above, there was a trend toward increase in secondarily generalized seizures at the lower doses (400 and 800 mg/day) and no effect in the higher doses, although there was great variability. In the present study there was a trend toward reduction, particularly at the higher doses (see table below). The data may suggest that only higher doses affect partial secondary generalized seizures. Although considering this is a post hoc analysis of a subgroup, the conclusions can only be made with caution. This data suggests an effect on the secondarily generalized seizures. It may also suggest that higher doses (1200 mg) may be required for control of such seizures, but such an analysis may be faulted as it is a subgroup analysis, without correction for multiple comparison, and likely underpowered.

Table 26: Standardized Seizure Frequency During the Maintenance Period by Seizure Type (ITT Population)

Parameter	Placebo (N = 220)	ESL 800 mg (N = 215)	ESL 1200 mg (N = 205)
Simple Partial During the Maintenance Period			
n	101	98	88
Mean	9.41	9.71	10.89
SD	13.739	19.432	19.293
Median	4.44	3.15	3.46
Min	0.3	0.3	0.3
Max	75.5	126.7	97.1
LS Mean (SE)	4.77 (0.53)	3.99 (0.44)	4.12 (0.49)
95% CI for LS Mean	(3.82, 5.93)	(3.20, 4.94)	(3.26, 5.20)
Log Difference in LS Mean	-	-0.17	-0.13
Unadjusted 95% CI for Log Difference	-	(-0.44, 0.11)	(-0.41, 0.14)
Unadjusted P value for Pairwise Comparison with Placebo	-	0.230	0.343
P value for Treatment-by-Region Interaction ^a	-	0.885	-
Complex Partial During the Maintenance Period			
n	164	158	148
Mean	9.21	9.40	7.44
SD	13.930	25.239	8.693
Median	4.94	4.39	3.95
Min	0.3	0.3	0.3
Max	101.4	294.0	42.0
LS Mean (SE)	5.18 (0.34)	4.74 (0.32)	4.22 (0.30)
95% CI for LS Mean	(4.55, 5.89)	(4.16, 5.41)	(3.67, 4.85)
Log Difference in LS Mean	-	-0.08	-0.19
Unadjusted 95% CI for Log Difference	-	(-0.25, 0.09)	(-0.36, -0.02)
Unadjusted P value for Pairwise Comparison with Placebo	-	0.343	0.031
P value for Treatment-by-Region Interaction ^a	-	0.523	-
Partial Evolving to Secondary Generalized During the Maintenance Period			
n	71	58	56
Mean	3.89	4.89	2.71
SD	7.592	10.480	2.743
Median	1.65	1.49	1.84
Min	0.3	0.3	0.3
Max	46.1	67.9	12.0
LS Mean (SE)	2.10 (0.24)	1.99 (0.24)	1.59 (0.21)
95% CI for LS Mean	(1.67, 2.62)	(1.55, 2.52)	(1.22, 2.05)
Log Difference in LS Mean	-	-0.05	-0.23
Unadjusted 95% CI for Log Difference	-	(-0.31, 0.22)	(-0.51, 0.04)
Unadjusted P value for Pairwise Comparison with Placebo	-	0.726	0.091

In her analysis Dr. Ling demonstrated that the presence of carbamazepine results in a decrease in the response to ESL. As noted above, the presence of carbamazepine was not considered a covariate in studies 301 and 302. Carbamazepine, however, is known to induce enzymes involved in ESL metabolism and thereby reduces exposure to ESL (see above). Dr Ling was

requested to perform an analysis on the primary endpoint in data grouped the presence or absence of carbamazepine as a concomitant medication. As may be expected, patients on carbamazepine exhibited a markedly reduced effect of ESL. This analysis, which was not included in Dr. Ling's review, can found in Dr. Podruchny's review. The label will recommend that adjustment in ESL dose. This data is complicated by the fact that in study 304, patients on carbamazepine were permitted to have their carbamazepine dose reduced during maintenance if intolerance was observed. Nonetheless, these data are consistent with what is known about the effect of carbamazepine on ESL metabolism and recommendations will be noted in the label that is described above.

Dr Ling concludes that "ESL 1200 mg dose group was statistically significantly different from placebo" and that "ESL 800 mg dose group was not statistically significantly different from placebo, but the results suggest a trend towards an improvement in standardized seizure frequency with this dose."

Dr Podruchny presented the Sponsor's evaluation of persistence of effect for study 304. Although this is a rough calculation, no obvious tachyphylaxis is apparent.

Global Efficacy Conclusions

I agree with Dr. Podruchny that the studies, particularly, study 301 and 302, suffered a number of issues regarding experimental design and execution. She has concluded that because of "a lack of confidence in data integrity" a CR action should be made. She does not believe that sensitivity analyses performed by Dr. Ling could correct for the problems encountered in this application. I, however, disagree. First I want note, as described above, that the errors in execution observed in these trials would likely be randomly distributed amongst treatment groups, and as such would be expected to reduce the ability detect a significant drug effect (reduced power) as it would be expected that these problems would increase background noise; in essence this will result in a bias toward the null. As best as I can see, no reviewer has argued that such errors could result in a false positive. Second, I believe that Dr. Ling's numerous sensitivity analyses, while not completely correcting errors, consistently pointed toward a therapeutic effect. Lastly, the third study, whose design was amended to address issues raised by this division, indicated a therapeutic effect of ESL. While alone not a reason for approval, it must be remembered that the principal active metabolite is shared by another approved drug, oxcarbazepine. In addition to the above, following 5 additional site inspection, OSI concluded that "data reliability for Studies 301 and 302 are less clear (with or without data from OAI sites), but the totality of findings (sponsor's audit, FDA inspections, consistent study outcomes) nonetheless support the acceptability of these two older studies as well (acceptable overall data reliability)." Also following 8 site inspections for Study 304, OSI concluded that the data from that study "appear reliable."

Another issue that must be dealt with regarding efficacy studies is that of the recommended doses. Studies 301 and 302 suggest that dosages 800 and 1200 mg daily are approximately equally efficacious. Yet study 304 failed to demonstrate a statistically significant effect at the dose of 800 mg daily (albeit the p value was borderline). This study indicated some degree of

dose response between 800 and 1200 mg daily when one examined simple magnitude of response. Moreover, upon the examination of the subgroup of patients with secondarily generalized seizure, and effect is only apparent at the higher dose. Also there is a substantial increase in adverse events when for those patients receiving 1200 mg daily as opposed to those on 800 mg daily. To me this may indicate that we cannot recommend the 800 mg dose as a recommended maintenance dose, but simply describe a range a dosages that should be targeted, with the final dosage dependent on a clinical response. This is not ideal, but titration to effect is not uncommonly used in the clinic.

8. Safety

Dr. Doi performed the primary safety review and Dr. Yasuda performed the supervisory review.

Database

The complete safety database for this application included a total of 4225 ESL-exposed patients who participated in 53 clinical trials: 847 were healthy volunteers, 1554 were subjects diagnosed with POS, and 1832 were diagnosed with other disorders including bipolar disorder, neuropathic pain, migraine, and fibromyalgia. Dr Doi notes that exposures met the ICH guidelines for a new medicinal entity. Indeed they were exceeded with 902 patients receiving ESL for at least 6 months (586 in epilepsy trials) and 686 receiving ESL for one year or greater (462 with epilepsy). Based upon Dr. Doi's tables, of the epilepsy phase 3 trials a total 825 patients received doses of 800 mg or greater, with an additional 984 receiving doses of 600 mg or greater in the non-epilepsy trials. Again, based upon Dr. Doi's tables, in phase 3 trials approximately 333 patients received a dose of 600 to 1000 mg for 26 to 52 weeks and 273 patients received these doses for greater than 52 weeks; these patient numbers are mutually exclusive. The number of patients receiving doses 1000 to 1400 mg for 26 and 52 weeks in the same population were 184 and 150, respectively. These exposures appear adequate. Of the phase 3 epilepsy safety database, sex was equally distributed. Mean age was in the late 30s with approximately 1% older than 60 years of age. Approximately 80% of patients were Caucasian, 8.5% Asian, 3.2 % black, and 1.2% Hispanic. Fifteen percent of patients studied were from Northern America and 34% from Eastern Europe, 22.9% from Latin America, and 14.1 % form Western Europe. Carbamazepine was the most common concomitant anticonvulsant in the phase 3 study (51%), followed by lamotrigine (24%), levetiracetam (17%), and other anticonvulsants.

The epilepsy program consisted of 4 Phase 3 controlled studies, five open label extension and 2 phase 2 controlled studies. Because of data integrity issues one phase 3 study (303) was not included in the ISS or Dr Doi's analysis with the exception of certain significant AEs (e.g. deaths and serious AEs).

Deaths

As per Dr Doi there were there were 11 post-randomization deaths in a total of 1322 patients studied (1766 patient-years) in the Epilepsy Phase 2/3 studies. On face the incidence of deaths in the drug group of the control phase 2/3 epilepsy trials were lower than that of placebo i.e.

the incidence in the ESL group was 0.08% (1/1313) and that for the placebo group was 0.36% (2/560). Dr. Doi notes only one case of SUDEP in the epilepsy database in a patient taking ESL, although she notes that this may have been confounded with status. Based upon this single case, the incidence of SUDEP is substantially lower the background rate in this population. Five additional post-marketing SUDEP cases were noted, which using the Sponsor's estimation is lower then background.

Seven deaths were noted in the controlled non-epilepsy trials. Three additional deaths were noted in these trials during the open label phase. Comparison of the total rate of deaths in placebo controlled trials for all non-epilepsy indications revealed no difference between drug and placebo groups.

Dr. Doi, examined causality of deaths. For the epilepsy trials a number of deaths were for events commonly associated with epilepsy (4 were thought to be related to seizures and 3 for drowning). Because of the deaths related to seizures Dr. Doi recommended that the efficacy reviewer examine the database for the exacerbation of seizures. Other causes of death in the complete studied population included brain edema (thought due to seizure)/arteriosclerosis, drowning/asphyxia, arteriosclerosis, coronary artery (in a patient with cardiovascular risk factors, status epilepticus, and astrocytoma (in a patient with recurrence of previous malignancy), and suicide (in 2 patients with one in a subject with a history of bipolar disorder and the other 73 days after the last dose of ESL), prostate cancer, bronchopneumonia, lung neoplasm malignant, gastric cancer/septic shock. There was no general pattern for these deaths. Based upon information and narratives of these cases both Drs. Doi and Yasuda do not believe these can be attributed to ESL. An additional 13 deaths were noted, some in ESL groups, but other in studies that are still blinded. I agree with their conclusion.

Serious Adverse Events

Of the complete phase 3 controlled/open label data base, 8.8% of patients on ESL suffered serious adverse events. The controlled epilepsy database revealed more SAEs in patients on ESL (5.3%) then on placebo (2.8%). More patients in the lower dose groups suffered SAEs then those in higher dose groups (7.1% for 400 mg, 7% for 800 mg, and 2.7% for 1200 mg), but as Dr. Doi discusses, this relationship must be interpreted with caution because of the limited number of cases. Only one patient in phase 2 studies suffered an SAE. Dr Doi performed a Forrest plot analysis of SAEs where she examined all SAEs where there was $\geq 0.2\%$ Risk Difference (Total ESL-Placebo) in Phase 3 Epilepsy Controlled Pool. This analysis revealed that the SAEs (preferred term) of ataxia, partial seizures, vertigo balance disorder, diplopia, nausea are events that fulfilled the latter criteria as well as the lower 95% confidence interval did not cross 0. This type of interpretation of the Forrest plot analysis is suggestive, but not definitely so (e.g. corrupted by the problem of multiple comparisons, etc.) of causality. Such SAEs are relatively common in the sodium channel blocking class of anticonvulsant agents (e.g. carbamazepine and phenytoin). As per Dr. Doi's analysis the following serious adverse events were identified in the epilepsy phase 3 controlled and open label trials (n (%)):

partial seizures	19 (1.6%)
vertigo	10 (0.8%)
fall	10 (0.8%)
vomiting	9 (0.8%)
convulsion	9 (0.8%)
ataxia	9 (0.8%)
nausea	8 (0.7%)
diplopia	7 (0.6%)
status epilepticus	6 (0.5%)
gait disturbance	6 (0.5%)
drug toxicity	5 (0.4%)
psychotic disorder	5 (0.4%)
head injury	5

(0.4%), loss of consciousness 4 (0.3%), asthenia 4 (0.3%), hemoglobin decreased 3 (0.3%), white blood cell count decreased 3 (0.3%), postictal state 3 (0.3%), epilepsy 3 (0.3%), pyrexia 3 (0.3%), drowning 3 (0.3%), dizziness 3 (0.3%), somnolence 3 (0.3%), speech disorder 3 (0.3%), confusional state 3 (0.3%), complex partial seizures 3, (0.3%), c-reactive protein increased 3 (0.3%), headache 3 (0.3%) and hyponatremia 3 (0.3%). Many of these serious adverse events are common to this class of anticonvulsant agents (vomiting, nausea, diplopia, vertigo etc.) or common to epilepsy (loss of consciousness, seizures etc.). Those that are believed to be causally related will be discussed in a section below.

A Forrest plot analysis in non-epilepsy studies did not reveal as clear of an effect when broken down by preferred terms (i.e. confidence interval analysis). Events, by preferred terms that occurred in 0.35 of patients and greater in both controlled and uncontrolled non epilepsy study included: mania 8 (0.4%), vomiting 8 (0.4%), nausea 6 (0.3%), pyrexia 5 (0.3%), unevaluable event 5 (0.3%), vertigo 5 (0.3%), dyspnea 5 (0.3%), and cardiac failure 5 (0.3%)

Dr. Yasuda notes that in the entire development program, there was 1 ESL case each of SAEs coded to: acute renal failure, acute respiratory failure, hyperthermia, ventricular arrhythmia, pancytopenia, septic shock, hepatic encephalopathy, blindness, Stevens Johnson syndrome, and toxic skin eruption. There were 6 ESL cases with SAEs of loss of consciousness and 2 cases of syncope. There were no ESL patients with SAEs of acute pancreatitis, acute hepatic failure (or hepatic failure), agranulocytosis, anaphylaxis, aplastic anemia, rhabdomyolysis, toxic epidermal necrolysis, torsades de pointes, ventricular fibrillation, or ventricular tachycardia.

Dr. Doi notes that the serious adverse events reported in the ongoing trials were similar to that of studies already completed. Post-marketing reports were also similar to those reported in the completed studies, with hyponatremia, seizures, neurologic effects (dizziness, ataxia, vertigo, aphasia, diplopia, altered state of consciousness, somnolence), and rash being most common.

As noted above, specific pertinent serious adverse events which are believed to be causally related to drug treatment are discussed by Dr. Doi and Yasuda and described in the section, below.

Dropouts and Discontinuations

Dr. Doi notes that in the Phase 3 epilepsy uncontrolled and controlled trials, over one-third of the ESL subjects (36.8%) withdrew from the studies; the most common reasons being discontinuation for adverse events (15.3%), withdrew consent (10.0%), and “other” (5.6%). In the controlled epilepsy trial there was an obvious dose dependency for discontinuations from adverse events with Placebo, 400 mg, 800 mg and 1200 mg experiencing 2.8%, 6.1%, 10.1%, 20.7% respectively. Dr. Doi notes that, according to the Sponsor, in controlled trials approximately one-third of all withdrawals occurred during the titration phase (first 2 weeks), with the remainder occurring primarily during the maintenance period. A similar pattern of withdrawal was observed in non epilepsy trials.

Examining Dr. Doi’s forests plots of TEAEs leading to discontinuation with $\geq 0.4\%$ Risk Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool, AEs preferred terms that meet these criteria but where the lower bond confidence interval did not cross 0 including the following: dizziness, ataxia, somnolence, nausea, vomiting, diplopia, vision blurred, asthenia and rash.

According to Dr. Doi’s calculations AEs, by PT, leading to discontinuation in $\geq 0.3\%$ of ESL subjects in Phase 3 Epilepsy Uncontrolled and Controlled Pool included: nausea (3.0%), vomiting (2.8%), ataxia (2.6%), diplopia (2.3%), somnolence (1.8%), vision blurred (1.1%), partial seizures (1.1%), vertigo (1.1%), headache (0.8%), asthenia (0.8%), fatigue (0.8%), rash (0.8%), gait disturbance (0.7%), dysarthria (0.6%), fall (0.4%), irritability (0.4%), depression (0.4%), tremor (0.4%), insomnia (0.3%), balance disorder (0.3%), nystagmus (0.3%), hyponatraemia 4 (0.3%). Examination of data for non-epilepsy trials reveals similar reasons of dropout. But, as noted by Dr Doi, the order (and frequency) of these differed. She believed these differences were likely due to the underlying diseases. These events are very similar to other anticonvulsant drugs.

No ESL subjects discontinued due to acute hepatic failure, agranulocytosis, anaphylaxis, aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, Toxic epidermal necrolysis, torsades de pointes, ventricular fibrillation, or ventricular tachyarrhythmia or tachycardia. Discontinuations in the ongoing trials are consistent with those reported for the clinical trials.

Pertinent Adverse Events

Hepatic Toxicity

Dr. Doi and Yasuda present data of a slight preponderance of elevated AST and ALT in controlled studies in both epilepsy and non-epilepsy trials. Dr. Yasuda’s table presenting total cases (and percent) is reproduced as below. There was only a modest difference between drug and placebo.

Test/Cutoff threshold	Phase 3 Epilepsy DB		Nonepilepsy DB Pool [^]	
	Placebo n=426	ESL n=1021	Placebo n=506	ESL n=1752
ALT				
ALT >3xULN	1 (0.2)	3 (0.3)	3 (0.6)	16 (0.9)
ALT >5xULN	1 (0.2)	0	0	7 (0.4)
ALT >10xULN	0	0	0	2 (0.1)
ALT >20xULN	0	0	0	1 (<0.1)*
AST				
AST >3xULN	1 (0.2)	1 (<0.1)	1 (0.2)	10 (0.6)
AST >5xULN	0	1 (<0.1)	0	4 (0.2)
AST >10xULN	0	0	0	3 (0.2)
AST >20xULN	0	0	0	2 (0.1)

In the complete database two patients with liver function test elevations had bilirubin elevations. These were examined more carefully so as to determine whether they fulfilled Hy's law (i.e. transaminase elevations > 3X ULN associated with total bilirubin > 2XULN and alkaline phosphatase < 2X ULN.) and if there may be potential causality. Both of these patients participated in non-epilepsy studies. These cases are briefly summarized as follows:

- A 57 year old female with a history of chronic pancreatitis, hypertension, and "transaminitis" that may have been association with a helminth infection 14 years prior to this event, developed severe vomiting and diarrhea on Study day 4. ESL was discontinued 2 days latter. Baseline liver enzymes were within normal limits (WNL). On the day of discontinuation ALT was 37X ULN, AST > 30X ULN and total bilirubin slightly > 2X ULN. ALP was 2.5X ULN. INR was within normal range. Dr. Doi notes no other potentially clinically significant (PCS) values for lab. Eight days after ESL discontinuation AST, total bilirubin and ALP returned to normal; ALT decreased to 1.7 XULN. All labs were within normal limits 1 month later. A thorough investigation for alternative etiologies was not performed by the investigator at the time of the event. Both Dr Doi and Yasuda believe this case meets Hy's law and represents a case of liver injury. I agree. Albeit, Dr. Doi notes that because alternative causes of Hy's law were not fully investigated, one cannot be 100% sure that drug caused this.
- A 57 year old male with a history of hepatic steatosis, diabetes, and hypertension, with ALP 1.8X ULN at baseline, developed elevated liver tests on Day 36 of ESL (AST 25X ULN, ALT 10X ULN, T bili 3.6X ULN, ALP 2.8X ULN but 1.6X baseline). No symptoms were reported. ESL was continued. ESL was continued but with some reductions in transaminase ALKPhos and BR. Dr. Doi believed these decreases were a result of dilutional changes, based upon the changes in other lab values. Dr. Doi believes that there were a number of confounders in this case including, including a prior history of alcohol hepatitis's, concomitant paracetamol during the study, lack of clear d challenge (AlkPos and BR remained elevated), and lack of a through investigation of causality (e.g. viral;). Nonetheless, both Dr Doi and Yasuda, believes that that a role of ESL cannot be ruled out. I agree that this is a confounded case.

In conclusion Drs. Doi and Yasuda consider, when conservatively evaluated, there are 2 Hy's law cases. With this in mind Dr. Doi calculated that the risk for such hepatic effects is 2/4225 subjects (in the All Studies Pool) or 4.7 per 10,000 subjects, and that the theoretical risk of severe DILI is 10% of that or 0.47 per 10,000 patients (based on the estimate from the "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation". Dr. Doi notes that this is less than the frequency of severe DILI for most drugs withdrawn from the market (according to the "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation"). Moreover Dr. Doi examined worldwide postmarketing data where she observed, with a database of with 12,279 patient years of exposure worldwide, there have not been any postmarketing cases of severe DILI reported by the sponsor. Both Drs. Doi and Yasuda believe that this should not prevent approval but that this information should be included label. I agree.

It was raised at DNP's labeling meeting wither this signal would require a REMS. There was a consensus amongst the DNP review group that REMS is not necessary. As noted above the

signal is no larger than other anticonvulsants, which do not have REMS. It was felt that the labeling and non-REMS MedGuide can serve sufficiently for risk amelioration.

Of note Dr. John Senior of OPE was consulted on this case. He agreed with Dr. Doi's and Yasuda's conclusions noting (referring to serious liver toxicity):

It will very likely be very rare, and will probably be preceded by early symptoms of liver dysfunction such as mild jaundice of the sclerae, dark urine, prolonged prothrombin time if tested, and elevated serum enzymes indicating cellular injury. Physicians who prescribe eslicarbazepine should be aware of this possibility, should immediately confirm, follow the adverse effect, interrupt administration of the drug while medical investigation is underway to determine the likely cause by ruling out the many alternative possibilities. This is just good medical practice, and should be mentioned in the labeling.

Serious Skin Reactions

Dr Doi describes a general increase in a variety of PTs related to skin reactions that may be immunologically mediated, and which were either classified as serious or resulted in discontinuations, that were more frequent in the drug treatment arm than the placebo arm in studies in epilepsy and non-epilepsy disorders. Examples of PT include rash, leukocytoclastic vasculitis, pruritus, drug eruption, rash –papular, toxic-skin eruption. Examination of narratives by Dr Doi in the experimental database revealed a single case of drug exfoliation with mucosal ulceration. This case had some elements of DRESS (e.g. elevated LFTs). The case was confounded by the use of Lamictal, and as per Dr. Doi did not strictly meet the criteria for probable Steven's Johnson syndrome (no biopsy and dermatology confirmation). The rash resolved on ESL dechallenge. The Sponsor also reported two cases of SJS in post-marketing database, but these cases are poorly described. The above described case and the fact that OXC, which was previously noted to share important metabolic constituents with oxcarbazepine and is labeled for this syndrome, led her to recommend Stevens Johnson syndrome Warnings and Precautions section. I agree. She also recommends that a postmarketing requirement to study possible risk factors including the association of alleles with severe cutaneous reactions.

Anaphylactic reaction/Angioedema

Dr Doe and Yasuda notes that no AEs were coded for anaphylaxis or angioedema, but there were cases that included hypersensitivity associated terms, including hypersensitivity, eye swelling, pharyngeal edema, and tongue edema. Examination of controlled epilepsy and non-epilepsy studies revealed such events had an incidence of <0.3% in the ESL arm and were not observed in the placebo arm. In the trials such events were described with PTs including tongue edema, urticarial, eyelid edema, hypersensitivity, and urticaria. Some events were considered serious and led to drug discontinuation and resolved with discontinuation. No trial events were associated with breathing problems, although a postmarketing event noted pharyngeal spasms and anaphylaxis. Both Dr Doi and Yasuda believe that information on such hypersensitivity response belongs in the Warnings and Precautions section of the label. I agree and will add that oxcarbazepine includes a section in Warnings and Precautions to anaphylactic reactions and angioedema.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Dr. Doi identified 3 cases in that met the RegiSCAR criteria for DRESS criteria; one of these cases was confounded with the concomitant use of antibiotics. Additional potential cases with elements suggesting DRESS were identified by Dr. Doi. No cases were identified in the postmarketing database. Dr Doi and Yasuda recommends including DRESS in the Warnings and Precaution section. Of note this adverse event is noted in the Warnings and Precautions section of oxcarbazepine. Since that time the Sponsor has provided the division with 10 additional cases, some with confounders, with elements of DRESS. Dr Doi feels that this should be included in the Warnings and Precautions section. I agree.

Neurologic Effects

Adverse events with the SOC Nervous System Disorders were common in the drug when compared to that of the placebo group in controlled epilepsy Trials (ESL 48.3%, placebo 31.2%) and non-epilepsy (ESL22.8%, placebo 13.4%) trials. Discontinuations for this class of adverse events followed a similar pattern in both types of studies. The predominate preferred terms classified under this SOC were dizziness, ataxia, vertigo, balance disorder, gait disturbance. Many episodes of vertigo and dizziness were associated with nausea and vomiting. Dr. Doi performed an analysis of falls, and observed a slightly greater preponderance in patients receiving drug and who exhibited the latter adverse events. Somnolence, fatigue and other related preferred terms appeared two times more common in grouped ESL data than placebo in the controlled epilepsy trials (placebo 13%, ESL 21%), These disorders also appeared to have a dose response relation. Dr. Doi notes that the neurologic events occurred more commonly during titration than maintenance and that the elderly were more prone to their occurrence. Cognitive related dysfunction (e.g. speech disorder, aphasia, memory impairment, amnesia, confusional state, disturbance in attention, disorientation, cognitive disorder, psychomotor retardation, apraxia, mental impairment, and Bradyphrenia) was also more commonly observed in the drug treatment groups by 4 fold, although their absolute rate of reporting was lower than the above neurologic events.

Both Dr. Doi and Yasuda believe this information should be included in Warnings and Precautions. These are very common events for anticonvulsants and are frequently described in the Warnings and Precautions section of anticonvulsants. They are included in the oxcarbazepine label. I agree with Dr. Doi's and Yasuda's suggestion.

Psychiatric Effects

Dr. Doi's examination of psychiatric adverse events yielded only a marginal difference between drug and placebo groups (slightly higher in drug). A retrospective analysis of suicidality using C-CASA revealed a signal was marginally greater in drug than placebo. A prospective analysis of suicidality by the C-SSR scale revealed slightly greater rates in the

placebo then drug. As per Dr. Yasuda the label will receive class suicidality language in the Warnings and Precautions.

Thyroid Function

Dr. Doi notes one case of “hypothyroidism” in the complete database. This case was not associated with clinical symptoms, but mild reductions in T4 and elevation in TSH. Examination of the epilepsy control database demonstrated a definite disparity in potential clinically significant low T4 and T3 values in epilepsy trials (e.g. T4 with ESL 13% and with placebo 4.1%), with a trend, but smaller in magnitude, in other disease studies. Mean values for T3 and T4 parameters seem to decrease in control trials, but no mean TSH was obvious. Dr. Doi believed this may be a result of a lag in TSH values, although that is conjecture. Shift table analysis of T3 and T4 were suggestive of reductions, but again conclusions regarding TSH were unclear. Dr. Doi performed other analysis to determine whether reductions in T3 and T4 might be clinically significant. First she examined how many patients in controlled epilepsy trial exhibited elevation in TSH associated with drops in T3 or T4. Dr Doi examined the percent for patients with low T3 and T4 who also had high TSH and found a high percentage of patients with these characteristics in drug then in placebo groups. I feel this is the wrong metric. The metric that one needs to look is the percent of patients in the full controlled study database with low T3 and T4 and high TSH. In this case there was not a great difference between drug and placebo. Thus, there was a background of 20/426 patients who fulfilled this requirement in the placebo group. The drug treated group did not experience a disparate effect; thus, the highest number of patients were observed in the 800 mg group with 18/415 patients fulfilling this criteria. To support her contention of a clinically relevant hyperthyroidism Dr Doi notes that the following labs and symptoms that are common to hypothyroidism were more commonly observed in ESL patients. These include hyponatremia, increased triglycerides, increased CPK and alopecia. But, I would note that the background of these in the general experimental population of patients exposed to ESL was high, and this likely confounds an association. Also it should be noted that hyponatremia is a known effect of this class of agents, which at the present while known to produce low T3 and T4 are not definitively known to produce frank hypothyroidism. ESL subjects who developed alopecia also experienced low free T4 or T3 levels. I do not believe that frank hypothyroidism has been observed. Both Dr. Doi and Yasuda believe information on hypothyroidism be added to the Warnings and Precautions of ESL labeling. I believe the information on the effect on T3 and T4, should be added to the label, but perhaps not at the level of Warning and Precautions. If at the level of the Warnings and Precautions, it should have low priority in the order.

I referred this issue to Dr. Kapcala of DNP for further elucidation. Dr. Kapcala is a neuro-endocrinologist. Dr. Kapcala examined the data in Dr. Doi’s review and searched the literature. He agreed with this reviewer that while free and total T4 and T3 appear to be suppressed, there is no definitive signal for hypothyroidism. Searching the literature, he discovered that phenytoin and carbamazepine, two very similar anticonvulsants, produce a similar spectrum of changes, without overt hypothyroidism. He notes that some believe that the suppression of free T3 and T4 appear to be a result of artifact of the method of measurement, and that a physical barrier method of measurement (e.g. equilibrium dialysis)

would correct for this artifact⁴. For this reason the Sponsor is going to be asked to examine this issue as part of a PMR. He notes that the total T3 and T4 on the other hand, appear to result from a different mechanism involving protein displacement of T3 and T4 by the drugs of interest. There may also be an effect of induction of metabolism by such drugs on T3 and T4. Patients with changes in these labs should however, still be carefully clinically evaluated, principally to ascertain that patients with such changes do not have underlying hypothyroidisms.

Hyponatremia

Hyponatremia was observed to be associated with treatment of ESL. There were cases of PCS values for hyponatremia in all controlled trials in the drug as compared to the placebo group. The percent of cases were directly proportional to dose. Some cases of hyponatremia were considered serious with Sodium values less than 125 mEq and neurologic symptoms including seizures, somnolence, headache, nausea, vomiting, memory impairment, balance disorder, and dizziness. Hypochloremia was associated with hyponatremia. Drug dose reductions or discontinuation usually resulted in the resolution of this adverse event. This finding is also observed with oxcarbazepine. Dr. Doi and Yasuda recommend presenting in the Warnings and Precautions section of the label, and I agree.

Vision

Visual changes, including diplopia and blurred vision, common to this class of drugs, were observed in the control studies and higher rates in drug groups than placebo (approximately 3 times more common). This will be included with other neurologic effects in the Warnings and Precautions.

Cardiac

Dr Doi notes no obvious differences in SOCs related to Cardiac Disorders. Moreover, there were no obvious un-confounded cases of serious cardiac events. Dr. Doi notes that the ECG data derived from clinical trials were not collected in the most rigorous fashion in that it appeared that only 75% of patients in the epilepsy trials had one post dose recording, presumably because of technical issues. The most noteworthy findings in the studies was the analysis of the PR interval, which revealed a small increased preponderance of PCS values of PR prolongation in the drug group as compared to placebo group. IRT reviewed the formal QT study and concluded no evidence of QT prolongation. The study, however, indicated PR prolongation, but the prolongation was not thought to be of a significant magnitude. Examination of Dr. Doi's review reveals only rare cases of lower level (first and second degree) AV block. There was a subtle signal for increased arrhythmias in ESL as compared to placebo treatment groups. But these were difficult to interpret. As Dr. Doi notes "there were differences in cardiac-related TEAEs seen in ESL subjects compared to placebo subjects, these

⁴ Surks and DeFesi, JAMA, 215, 1495-1498, 1996

differences were small and difficult to attribute to ESL (especially in light of the baseline differences in prior cardiac history and cardiac risk factors in the nonepilepsy population).” Dr. Yasuda recommend information on PR prolongation is included in the label. I believe this should go in section 6.

Seizures

Dr. Podruchny examined the database to determine whether seizures were a potential adverse event. This is very difficult considering the fact that the primary endpoint is seizure count and this population would be expected to have seizures. Some of the more salient observations are that in controlled trial status epilepticus appears more common in the placebo groups. No new seizure types; i.e. primary generalized seizures were not reported in a patients with only partial onset seizures. In some studies, although not all, more seizures were reported as serious AEs in the 800 mg dose group. I believe this data is difficult to interpret, but, in sum, do not suggest a worsening of seizures.

Common Adverse events

Because of issues of data integrity a number of different datasets were provided that described adverse events prior to and after a variety of audits. Dr Doi determined that the ADEVENTX dataset should be the most appropriate. Data transcribed from Dr. Doi’s analysis of the epilepsy controlled phase 3 studies where events were $\geq 2\%$ and more frequent than placebo in any dose group are presented in the table below. The most common adverse events are those referable to the nervous system. Thus, dizziness, somnolence, diplopia, vision blurred, and fatigue are rather common treatment related events, with a relatively large teraetment effect (drug-placebo group). Headache was also a very common AE. All of these and many of the other common AEs exhibit dose dependency, with a rather substantial increase in risk at 1200 mg/day when compared to 800 mg/day. Thus, there was an approximately 40% to 80% increase in incidence when the 800 mg dose is compared with the 1200 mg dose. Gastrointestinal adverse events were also commonly observed. This spectrum of adverse events is very common for this class of drugs.

MedDRA System Organ Class Preferred Term	Placebo n=426 %	ES			Total ESL n=102 1
		400 mg n=196	800 mg n=415	1200 mg n=410	
Subjects with any TEAE	58	67	71	78	7
Cardiac disorders					
Bradycardia	0	2	0	<1	<
Ear and Labyrinth disorders					
Vertigo	<1	3	2	6	4
Eye disorders					
Diplopia	2	7	9	11	1
Vision blurred	1	5	6	5	5
Visual impairment	1	0	2	1	1
Gastrointestinal disorders					
Nausea	5	9	10	16	1
Vomiting	3	5	6	10	7
Diarrhea	3	2	4	2	3
Constipation	1	4	2	2	3
Abdominal pain	1	2	2	2	2
Toothache	1	2	<1	2	1
Gastritis	<1	0	2	<1	1
General disorders/administration site conditions					
Fatigue	4	3	4	7	5
Asthenia	2	2	2	3	3
Gait disturbance	<1	2	2	2	2
Irritability	<1	4	1	1	1
Edema peripheral	1	0	2	1	1
Infections and Infestations					
Influenza	2	4	2	2	3
Urinary tract infection	1	1	2	2	2
Injury poisoning and procedural complications					
Fall	1	2	3	1	2
Contusion	1	2	1	1	1
Investigations					
Weight increased	2	4	1	2	2
Blood CPK increased	1	4	1	1	1
Blood cholesterol increased	<1	2	1	<1	1
Blood pressure decreased	<1	2	<1	<1	1
Blood pressure systolic decreased	0	2	0	<1	<
Metabolism and nutrition disorders					
Hyponatremia	<1	1	2	2	2
Musculoskeletal & connective tissue disorders					
Arthralgia	1	2	2	0	1
Nervous system disorders					
Dizziness	9	16	20	28	2
Somnolence	8	13	11	18	1
Headache	9	12	13	15	1
Ataxia	2	4	4	6	5
Balance disorder	<1	1	3	3	3
Tremor	<1	1	2	4	3
Dysarthria	0	0	1	2	1
Memory impairment	<1	1	1	2	1
Nystagmus	<1	1	1	2	1
Psychiatric disorders					
Depression	2	3	1	3	2
Insomnia	1	2	2	2	2
Nervousness	<1	2	<1	1	1
Reproductive system/breast disorders					
Menorrhagia	<1	2	<1	0	<
Respiratory, thoracic & mediastinal disorders					
Cough	1	0	2	1	1
Skin & subcutaneous tissue disorders					
Rash	1	1	1	3	2
Pruritus	1	2	1	1	1

Cross Discipline Team Leader Review

Alopecia	1	2	<1	1	1
Hyperhidrosis	<1	2	<1	<1	1
Vascular disorders					
Hypertension	1	2	1	2	2

Clinical Laboratories

Some additional clinical chemistry labs were observed to be affected, including those described above. These appeared to have less clinical significance. Thus there was a small signal for elevation of CPK, but without any indication of rhabdomyolysis. There was also no obvious effects on urinalysis labs were observed.

Dr. Doi noted a slightly greater tendency towards a higher frequency of decreases in hemoglobin and hematocrit indices in patients on drug as compared to placebo. While there were a few hematologic events resulting in discontinuations or classified as serious, examination of causality could not attribute this to ESL. No events were coded as granulocytosis or aplastic anemia. Dr. Doi recommends continued pharmacovigilance, looking for blood dyscrasias.

Drs. Doi and Yasuda note that because bicarbonate values were not collected in the large phase 2 and 3 studies submitted in this application, a definitive conclusion on the effect of ESL on acid-base balance or bicarbonate values cannot be made. For this reason there was a consideration of requesting a PMR to to examine this issue. Upon a further review of ongoing studies and additional information requests, Dr. Doi identified studies, containing this information that allowed her to conclude a lack of effect. Of note, unlike some other anticonvulsants, ESL is not a carbonic anhydrase inhibitor.

Vital Signs

Temperature was not evaluated. No obvious effect was observed on blood pressure. Orthostatic changes were observed in some studies, but the small number of observations does not allow a conclusion. PCS values for weight loss were very slightly more common in drug group, but these effects were small and Dr Doi and Yasuda believe no conclusions can be made fro this reason.

Other

No obvious carcinogenicity signal was observed. Dr. Doi notes that the small number of pregnancies did not allow any definitive conclusions regarding fetal toxicity and teratogenesis. I would also add, at least with regard to epilepsy studies, most patients were on multiple anticonvulsants, which likely confounds the data.

Conclusions

While this application suffered many data quality issues, Dr Yasuda notes, that with requested clarifications and analysis the application was sufficiently complete to make a determination of safety for adequate labeling. Dr. Yasuda and Doi do not believe that any safety issues were identified that would prevent approval; although labeling is required. I agree.

9. Advisory Committee Meeting

Not requested.

10. Pediatrics

The Sponsor submitted a PPSR, which because of time restrictions have not yet been reviewed. Representatives from this division along with those from OCP and statistics met with the PERC on 19/16/13. Based upon that meeting the following studies and issues are agreed upon and should be specified as necessary to fulfill PREA:

- A waiver will be granted for patient efficacy studies 1 month and younger because there are few patients who can be definitively diagnosed with this condition making such a study highly impractical.
- Adequately controlled, randomized, prospective safety/efficacy studies with extension examining POS would be required, but may be deferred, for patients > 1 month to (b) (4) years because the drug is ready to be approved in adults. This should be accomplished through two studies, one using a diary based endpoint for children older than 2 (or 4) years old and the other using Video/EEG based endpoint for younger children (< 2 or 4 years old). The studies should include a subgroup analysis on the effect concomitant enzyme inducing drugs (e.g. carbamazepine, phenobarbital, and phenytoin) on efficacy and safety. The studies should include an open label extension phase to collect long term safety data.
- One PK and tolerability studies in epilepsy patients > 1 month to <24 months of age. (b) (4)
[Redacted]
Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohorts. (b) (4)
[Redacted]
- Following the Pharm/Tox study and guided by such studies, the Sponsor may proceed with PK studies in children <2 years and the efficacy/safety study in children > 2 years simultaneously. Following the PK study in children < 2 years, and guided by the information gleaned from the study, the efficacy study in children < 2 years can be initiated. Long term extension safety studies can continue from the efficacy/safety studies in their respective age groups.

(b) (4), (b) (5)

[Redacted]

11. Other Relevant Regulatory Issues

Data Integrity

The principal reason for the prior CR determination revolved around issues of deficiencies related to the conduct and documentation of the studies. These conclusions came largely from inspections, although Dr. Podruchny, the medical reviewer of the original NDA, noted a number of irregularities that complicated her review of safety and efficacy data. At that time 4 inspections were carried out, 2 in each of 2 pivotal studies (Study 301 and 302). Two sites (Investigators Dr. Danilo Hodoba and Dr. Carmen Diaz-Obregon), one in each of the two studies, were considered unreliable. These sites required an “Official Action Indication” (OAI) outcome. As per the CR letter dated 4/30/10 data from sites failed in the following categories:

- “Failure to conduct the study(ies) according to the signed investigator statement and the investigational plan [21 CFR 312.60].
- Failure to prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)].
- Failure to document and report adverse events to the sponsor [21 CFR 312.64].
- Failure to prepare and maintain adequate drug accountability records of disposition of the drug, including dates, quantity, use by subjects, and amount returned by each subject [21CFR 312.62(a)].”

In the process of the prior review, during the review cycle, the Division requested that the Sponsor perform audits on additional sites. Review of these reports OSI reviewer, which could not be completed in the review cycle, nonetheless suggested “GCP violations and noncompliance with commonly accepted good clinical practices and federal regulations.” These audits were not complete. Additional requests were made in the CR letter including:

1. Provide the additional information including SOPs in place during the study performance, description of QA program with respect to CRO oversight, corrective actions taken and outcome for audited sites and, a list of non-compliant sites and actions taken to ensure compliance.
2. “...provide assurance that safety and efficacy data obtained in Studies BIA-2093-301 and BIA-2093-302 are reliable...suggest ...a third party, perform additional audits of clinical sites that enrolled subjects in these studies.”

The CR letter did express that “it is possible that additional studies may be required.”

As noted above, an additional study was added to the present Sponsor’s response. This study was already in process during the prior review, but was amended to answer some of the issues raised in the clinical and statistical review (the addition of North American sites and the of daily diaries).

OSI Review

Dr John Lee performed the OSI review of this application. Dr Lee notes that third party audits were performed for nearly all sites in studies 301 and 302 and half the sites in study 304. In addition to audits the Division and OSI agreed to inspections of a large number of sites. Thus,

5 additional sites from Studies 301 and 302 were inspected and 8 sites from Study 302 were inspected. Some of these inspections overlapped (i.e. the same site used for more than one study). Dr. Lee notes that

a major consideration in selecting the clinical study sites to be inspected were original audit outcomes as well size of the site, multiple studies at same site, and world-wide site distribution.

Dr Lee notes that no additional OAI actions were taken for sites associated with Studies 301 and 302 nor were there any such actions for Study 304. Following his evaluation of the additional audits and inspections Dr Lee concludes the following:

“The sponsor's oversight appears to have been more real-time for Study 304 (closer monitoring while the study was on-going) and more retrospective for Studies 301 and 302 (90% of study sites audited). In either case, the sponsor claims adequate GCP compliance for all three studies, as (also) supported by their claims of consistent outcomes for Studies 301, 302, and 304.

Study 304 was conducted in the US and worldwide (Canada, South America, South Africa, Australia, Asia, and Europe). Adherence to GCP appeared adequate for all sites inspected and not appreciably different between US and non-US sites.

The FDA findings (limited to few sites) were consistent with the sponsor's (more extensive) audit findings. Deficiency frequency did not correlate with seriousness. The FDA findings served to validate the sponsor's findings. Sites with frequent deficiencies (per sponsor audit) were not consistently VAI (or OAI) per FDA inspection.

Study sites in Studies 301 and 302 appear to be at higher risk for GCP non-compliance than those in Study 304. The overall rate of GCP compliance across all clinical studies and sites appears to be sufficient to support this NDA, with greater confidence for Study 304 than for Studies 301 and 302.”

Dr. Lee attributes one of the differences between the seriousness of the first series of inspections and the present to sampling error and the fact that the distinction between a VAI and OAI action is not always clear.

Dr Lee concludes:

“The data from Study 304 appear reliable based on direct inspectional findings. Data reliability for Studies 301 and 302 are less clear (with or without data from OAI sites), but the totality of findings (sponsor's audit, FDA inspections, consistent study outcomes) nonetheless support the acceptability of these two older studies as well (acceptable overall data reliability), as secondary supplemental studies to the primary pivotal Study 304.”

Dr. Lee notes in his review that the inspection of the Sponsor has not been received in final form, and an addendum to his review. Include in these were laboratory data missing from the ISS datasets that required 2 resubmissions to correct, many discrepancies, programming errors, coding omissions, key information missing from the narratives (including a death that was included in a previous version of the narratives), and narratives of subjects with adverse events

of special interest missing from the ISS. Identification of these led to numerous requests to the Sponsor and subsequent Sponsor's clarifications by DNP's review team.

Safety Review

Dr. Doi identified numerous deficiencies in the safety section of this response to CR. This required numerous communications and requests to the Sponsor that resulted in over 23 safety information amendments. The information that required clarification and correction included laboratory data missing from the ISS datasets and required 2 resubmissions to correct, many discrepancies, programming errors, coding omissions, key information missing from the narratives (including a death that was included in a previous version of the narratives), and narratives of subjects with adverse events of special interest missing from the ISS. Dr Doi notes that other yet unidentified deficiencies cannot be ruled out, albeit she leaves the final decision on the acceptability of the data base to others. Dr. Yasuda notes that that despite the inability to identify other safety issue that "that the submission along with the amendments responding to Dr. Doi's many and important information requests allowed for a review of the safety of ESL." Dr. Doi has expressed a similar view in many of our internal meetings. I agree with this conclusion.

Efficacy Review

Dr. Podruchny, the MO who performed the efficacy review (see above), notes there were an inordinate number of requests for additional information in this application. She points to CSS, CMC, safety and her own requests that numbered 5 to 6. One such example in her efficacy review are inclusion of duplicate entries of seizures (i.e. seizure on the same date and time repeated in the dataset listing) and the identification by DNP of the use of both types of diaries in part 1 of the study in one subject (subjects were to use one or the other depending on time of entry into the study). To further support her contention of the difficulty of this application she notes that the Sponsor's first response to the CR, which resulted in an incomplete response, required additional communications till the final application was considered complete. I would note that even then the final Complete Response required additional clarification. Dr. Podruchny also notes issues that were described in sections above, for which there were sensitivity analyses, including hard coding and daily versus event diary issues. Dr. Podruchny also points the initial OSI review which was rather problematic (see OSI review above). Her review was, however, completed before OSI provided the Division with their final review, although she does acknowledge that she had prior knowledge that the inspections may be favorable. Because of these findings Dr. Podruchny concluded that the Agency "issue a Complete Response letter to the Sponsor of Eslicarbazepine Acetate (ESL) due essentially to a lack of confidence in data integrity at this time and uncertainty that the processes in place to conduct and/or oversee the trials in a corrective manner and present accurate data functioned/function effectively."

CDTL's Conclusion

I am not in complete agreement with Dr. Podruchny. My retort can be found in Section 7 (Clinical/Statistical- Efficacy). But I would like to note that the Safety team believes that an approval action can be taken. Moreover, the new OSI reviewer felt there study 304 can be relied upon and that although there were issues identified for studies 301 and 302 the totality supports the acceptability of these older studies. I do agree that the older studies were executed and presented in a sloppy fashion and the newer study less so. Although I must note that I have not seen such a detailed examination of an application for data integrity issues (e.g. almost complete third part audit as well as a large number of inspections) before, albeit such an examination was deserved. My feelings are that sloppiness and not willful obscuration was the primary inadequacy. Sloppiness introduces noise into experimental design making it more difficult to identify a positive signal. Therefore I am more concerned about issues of safety than that of efficacy. Nonetheless, our safety reviewers felt that the application was adequate for approval and labeling. Moreover, despite the sloppiness efficacy was observed, although not always with a robust p value. This is what would be expected form a study where noise is introduced.

CSS and Drug Scheduling

Dr. Lerner performed the CSS review. Dr Lerner notes the limitations of the data because of data integrity issues (although the reader should also see the Safety section of this review). The issue raised in her review principally involved issues of drug withdrawal, and therefore that of drug dependence. Therefore, the label will not comment on dependence and Dr. Lerner is asking for the following PMR: “perform a human dependency study in healthy volunteers.” She notes that CSS should be consulted on the protocol. It should be noted that Dr. Lerner agrees with Dr. Podruchny that the application should not be approved. This was based upon her examination of safety issues surrounding her CSS review. Nonetheless, Dr. Doi and Yasuda came to a different conclusion, even though her review partially overlapped in content.

In an addendum on 10/16/13 Dr. Lerner identified a number of cases of overdoses that were misrepresented in the ISS. She notes that the number of cases of overdosage was underrepresented in the ISS for the postmarketing data. According to an ISS table, 24 cases are identified, when she notes there were actually 114 cases. I asked Dr. Doi to examine this issue further. Dr. Doi notes that the Sponsor argues that this inconsistency was a result of the way an overdose was coded. Two coding methods were used. A conservative coding reported an overdose if the drug was prescribed by a physician at a dose greater than the labeled dose. A more liberal method coded overdose only if the patient had taken more than that which was prescribed. While this appears to explain the error on face, there is still some confusion as to what the ISS tables represent. Nonetheless, Dr. Doi noted that on face it does not appear that any no unusual or unexpected adverse events were identified associated with these cases; although specific information was limited only to cases for which narrative were provided (e.g. serious cases). Dr. Doi will be entering this information into the record in the form of emails exchanged with me.

Proprietary Name

The proprietary name, Aptiom, was found acceptable. DMEPA's analysis showed no significant risk of confusion with other marketed products. DDMAC did not consider the proprietary name as promotional.

Financial Disclosure

Dr Podruchny, the medical reviewer, examined the information provided in the original submission along with later requested additional information (7/31/09) and concludes the information "appears acceptable." She notes one potential conflict the new study (study 304) for one sub-investigator (b)(6) who received greater than \$25,000, presumably in consulting fees. (b)(6) contribution to this study, however, was minimal; she randomized (u)(u). This would not influence the study outcome.

It is noteworthy that the Sponsor was unable to obtain financial disclosure on investigators from 6 sites, which included a total of 65 patients. Two of the six sites, including 41 patients, participated in study 303. Data from this study was considered corrupted and therefore was not an important factor in the final decision for approval. Therefore, any potential conflict would not affect the final decision. Of the remaining 24 patients, 18 were from one site (b)(6). The 24 patents account for less than 2% (24/1227) of the complete controlled trial database (Studies 301, 302 and 304). The small percentage of the number of patients would not influence the final results and regulatory conclusions.

12. Labeling

The team met a number of times to edit the label. See the body of this review for labeling recommendations. The reader may also refer to the final negotiated label in the action letter.

13. Recommendations/Risk Benefit Assessment

I will recommend for approval for reasons cited above. The present drug appears to have similar efficacy and safety features of already approved drugs (see above). I agree with Dr. Doi that pharmacovigilance is required for hematologic safety issues and would also add thyroid to the list of pharmacovigilance issues. Further pharmacovigilance issues added following discussions with the safety team are AV heart block and liver toxicity. A REMS is not necessary.

The following PMRs are indicated:

- Those related to PERC issues, including PK, Pharm/Tox and efficacy/safety studies described in Section 10 (Pediatrics) for children older than one month.
- A dependence study described in Section 11 (Other Regulatory Issues).

- Safety study to investigate the pharmacogenomics of serious skin reactions described in Section 8 (Safety).
- A study to investigate the measurement artifact of in the evaluation of free T3 and T4.

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/s/

NORMAN HERSHKOWITZ
11/05/2013