CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202067Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10/19/11
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202067
Applicant	Lundbeck Inc.
Date of Submission	12/23/10
PDUFA Goal Date	10/23/11
Proprietary Name / Established (USAN) names	Onfi/Clobazam
Dosage forms / Strength	Tablet 5, 10 and 20 mg.
Proposed Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients $\geq$ 2 years of age.
Recommended:	APPROVAL

Cross Discipline Team Leader Review

1. Introduction

The Sponsor has submitted an NDA for Clobazam (CLB) as a treatment for seizures associated with Lennox-Gastaut syndrome (LGS). CLB is a benzodiazepine that has been approved for the treatment of anxiety and epilepsy in over 100 countries since 1970.

LGS is a relatively uncommon and serious epileptic syndrome which begins at childhood, 3-8 years of age, and is associated with multiple seizure types including, but not limited to, tonic, atonic, myoclonic and atypical absence. Seizures causing falls are a very dangerous aspect of this disorder. Such events can lead to serous head injury and requires the wearing of protective helmets. These are referred to as "drop attacks" and are associated with tonic, atonic or myoclonic seizures. Seizures in LGS are considered to be intractable and are largely generalized in nature. LGS is associated with an encephalopathy in 78 to 96 percent of patients. LGS is associated with a distinctive EEG pattern, which helps in its diagnoses. LGS is frequently preceded by infantile spasms. Although it is a single syndrome entity, it may be associated with a number of causal etiologies (e.g. perinatal hypoxia or ischemia, cerebral infections tuberous sclerosis etc.) or it may be cryptogenic, without any identifiable etiology. Prognosis for complete seizure freedom is poor, with greater than 80% of patients suffering with seizures despite "optimal treatment." Patients may maintain characteristics of the Lennox-Gastaut syndrome as they mature into adulthood, but others may develop other sorts of seizure disorders.

There are currently, five antiepileptic drugs (AEDs) approved for seizures associated with LGS including clonazepam, felbamate, lamotrigine, topiramate, and rufinamide. A number of other anticonvulsants, which are not specifically labeled for LGS, are used as well, as is a ketogenic diet and vagal nerve stimulation.

2. Background

As noted above, LGS is a relatively uncommon syndrome and makes up 3-10% of childhood epilepsies, depending how the syndrome is defined. Because of this, it was granted orphan status in December, 2007.

The CLB IND dates back to 2005. A primary issue that was identified early in its development was the need to have sufficiently long studies so as to examine for the possibility of tachyphylaxis as this is a potential problem in seizure control for the benzodiazepine class and has been observed in animal models. As a result of this, studies were to be adequately long and separate analyses for the tachyphylaxis phenomena were to be carried out.

3. CMC/Device

While a number of problematic issues were identified in CMC's initial review, additional information provided by the Sponsor resolved all such issues. This information is described in an addendum to the initial review. Approval is recommended by the CMC reviewer, Dr Khairuzzaman.

4. Nonclinical Pharmacology/Toxicology

Dr. Edward Fisher performed the Pharmacology/Toxicology review with Dr. Lois Freed performing the supervisory review.

Dr Fisher notes that the anticonvulsant effect is likely a result of its action at the benzodiazepine receptor. The predominant metabolite of CLB, N-desmethylclobazam (N-CLB), also binds to the benzodiazepine receptor and, when tested in a pentylenetetrazole model of epilepsy, was "somewhat less potent than CLB." As in humans (see below), the N-CLB metabolite is found in serum at higher levels in experimental animals than is CLB. Animal models in epilepsy demonstrated some degree of tolerance to the anticonvulsant effect of CLB. This was the subject of an important clinical endpoint (see the Clinical/Statistical Efficacy section below). Dr. Fisher notes that there was a paucity of good toxicokinetic data.

The original non-clinical toxicity studies were performed before 1975 and, in general, are not up to the current GLP standards. As a result, the Sponsor was requested, prior to the NDA submission, to provide additional non-clinical studies. The Sponsor included additional studies. The following sections describe salient aspects of toxicology.

General Toxicity

Dr. Fisher notes that the general non-clinical studies are not up to current standards. A number of deficiencies are outlined for these studies including, but not limited to, lack of adequate long-term toxicokinetic bridging studies for mouse, rat, or rabbit, incomplete histopathology examination in some studies, absence of pertinent data (e.g. absence of line listings and summary pathology tables), etc.

Salient findings in chronic studies are summarized as follows. In rats, hepatocellular hypertrophy and thyroid atrophy (as evidenced by a decrease of the follicular colloid and cuboidal follicular cells) were noted. Potential withdrawal seizures were noted in dogs. Alkaline phosphatase was increased in the 6-month and 1-year dog studies, but histopathological changes were limited to hepatocellular eosinophilic cytoplasmic inclusions in the 6-month study at 80 mg/kg. Neurobehavioral symptoms, as expected for a benzodiazepine, were observed in animal studies. In general, the above findings were not considered problematic.

While these studies are not up to current standards Dr. Fisher concludes, contingent upon clinical approval of human data, and considering the wide use of this drug and the seriousness of the disorder, that the information could be generally considered adequate for approval. Notwithstanding this decision, Drs. Fisher and Freed believe that the absence of toxicokinetic data is a serious deficiency in the Sponsor's application, but also believe that this can be provided post-approval as part of PMR carcinogenic studies, which will also be requested (see below).

Carcinogenicity

In vitro genetic toxicology and carcinogenicity studies proved to be unremarkable.

Mice and rat carcinogenicity *in vivo* studies revealed an increase in hepatocellular adenomas in mice. This finding was not statistically significant and no hepatocellular carcinomas were identified. Rat *in vivo* carcinogenicity studies revealed a dose-related increased incidence of thyroid follicular cell adenomas in males. Thyroid follicular cell carcinomas were not observed nor were any other tumors. A number of factors compromised these studies including, but not limited to: 1) loss of animals because of mortality and resulting low sample size that compromised the statistical validity (insufficient number and time exposure); 2) lack of the reliability of the method of dosing used (dietary dosing); 3) the fact that official GLP standards were not followed (study preceded the GLP regulations), 4) as legacy studies there was a lack of an electronic database, which had to be created by the Sponsor and contained fewer reported tissues. The Carcinogenicity Assessment Committee (CAC) concluded that there were no significant drug-related neoplasms in mice and that the increase in thyroid follicular cell adenomas in mouse was drug-related. The CAC concluded the studies were inadequate by today's standards.

Dr Fisher notes that the findings in mouse and rat carcinogenicity studies of CLB are generally consistent with what has been clinically reported. Dr. Fisher also identified other benzodiazepines, which are marketed, that lack substantial carcinogenicity data. Both Drs. Fisher and Freed believe that, considering the serious nature of the disease, the problematic carcinogenicity studies should not hold up approval of this drug, but that supplemental studies should be required as a PMR. These studies should also include toxicokinetic data, which was noted to be lacking (see above).

Reproductive and Developmental Toxicity

Developmental studies demonstrated a potential increased incidence of cleft deformities in mice. This finding however was unclear as this species is prone to such deformities, and it is unclear how maternal stress may have factored into this observation. Human reports of cleft deformities have been made in the past for benzodiazepines in general, but Dr. Fisher specifically notes that more recent publications have failed to confirm this. While Dr. Fisher concludes that there was no evidence of a strong teratogenic potential in the studies, the studies

had a number of shortcomings, not having been performed according to current standards. Thus, dosing periods did not include the entire period of organogenesis, there was inadequate dosing and the lack of dosing justification, and there was inadequate evaluation of some endpoints (e.g., neurobehavioral and immunological). For reasons noted above, it was felt that these inadequacies should not hold approval up, but should be the subject of a PMR.

5. Clinical Pharmacology/Biopharmaceutics

General PK Issues

The primary Clinical Pharmacology reviewer's were Drs. Ta-Chen Wu and Seogeun Julia Cho. Dr. Angela Men was the Clinical Pharmacology team leader.

CLB pharmacokinetics are linear throughout its recommended therapeutic range. Relative bioavailability, compared to solution, is 100%. Only a small food effect was observed, and crushing pills had no significant effect on absorption. CLB is extensively metabolized with only 2% of CLB identified in the urine. The major metabolite of CLB is N-desmethyl clobazam (N-CLB), which is believed to be active and exists at concentrations many times that of CLB in serum. N-CLB represents 62.5-73.8 % of the total metabolic products in the urine. N-CLB formation is principally mediated through CYP3A4 metabolism but, to lesser extent, through 2C19 and 2B6 metabolism. N-CLB is metabolized, mainly by CYP2C19. Plasma protein binding of CLB and N-CLB is moderate (88.9-77.7% and 74.1-69.1%, respectively). The half lives of CLB and N-CLB are 36-42 hours and 71-82 hours, respectively.

Special Populations

In a number of special conditions where elimination may be slowed, PK has recommended that dosing adjustments be made. These adjustments recommend a slower titration and reevaluation of the clinical condition following the achievement of a half dose targets. There is then an allowance to achieve a full dose if necessary based upon the clinical effect observed at the lower target doses. These clinical conditions are described as follows:

- Because population PK reveals a lower clearance in the elderly, dosage adjustments are recommended. No such adjustment is recommended based upon race, ethnicity or sex.
- A single case study provided by the Sponsor suggested that dose adjustment is not needed in severe renal disease. This was deemed as inadequate, and our clinical pharmacologists recommend that dose adjustments may be needed in such patients. There is no information available on whether CLB is dialyzable, although the clinical pharmacologists believe it may not be. This absence of information will be described in the label. No dose adjustment is being recommended for mild or moderate renal impairment as Cmax and AUC are not significantly changed, as determined in a dedicated renal impairment study.
- Data on hepatic impairment was based upon one published paper, which included a limited number of patients. Although little effect was observed in mild and moderate liver impairment, because of the limited nature of the data, the above noted dosing

adjustment is recommended. Even less data was available in this publication for severe liver disease, and, for this reason, no dosing recommendations are given.

- Because genotypic poor metabolizers of CYP2C19 experience 3-5 fold higher N-CLB concentrations, as compared to the wild type gene, and N-CLB is an active metabolite, dosing adjustment is being recommended. (b) (4) [redacted] The Clinical Pharmacology reviewer, however, point out that one Japanese study did find differences in adverse events in the different genotypes. For this reason, the above dose adjustments are being recommended.

Drug Interactions

In vivo Studies have shown that CLB is an inhibitor of CYP2D6, indicating that drugs metabolized by this enzyme require dose reduction when used with CLB. Mild CYP3A4 induction was identified, but this effect is sufficiently small not to require dose adjustment. As some hormonal contraceptives are metabolized by this enzyme, back-up non-hormonal forms of contraception will be recommended.

CLB and N-desmethylclobazam do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

As noted above, N-CLB is principally metabolized by CYP2C19. Based upon extrapolation from genomic data, PK concluded that strong and moderate inhibitors of CYP2C19 may result in increased exposure of CLB's active metabolite, N-CLB. For this reason a consideration of dose reduction is recommended when CLB and either strong or moderate CYP2C19 inhibitors are used concomitantly.

The effect of a variety of anticonvulsants (phenobarbital, phenytoin, carbamazepine, valproic acid, phenobarbital, phenytoin, and carbamazepine, felbamate and oxcarbazepine) on CLB was examined through pop-PK. These anticonvulsants were not found to significantly affect the metabolism of CLB.

Clinical Pharmacology Conclusions

The Office of Clinical Pharmacology recommends approval of CLB. They have no phase 4 commitments.

6. Clinical Microbiology

Does not apply.

7. Clinical/Statistical- Efficacy

Dr. Phillip Sheridan and Dr. Ohid Siddiqui performed the clinical and statistical review, respectively.

Two principal studies have been submitted by the Sponsor to support the requested indication: 1) a pivotal study, OV-1012 and, 2) a supportive study OV-1002.These will be discussed in their respective sections below. This is supplemented by a single, ongoing, open-label study, OV-1004.

OV-1012

This was a multicenter, randomized, double-blind, parallel-group, multiple-dose arm, placebo-controlled study. The study consisted of a 4-week baseline period, a 3-week titration period and a 12-week maintenance period, followed by a 2- or 3-week taper period. The protocol called for a placebo arm and 3 active drugs dosing arms (low, medium and high dose). Daily target doses for each arm were approximately 0.25 mg/kg, 0.5 mg/kg and 1.0 mg/kg, in the low-, medium- and high-dose groups, respectively. To accomplish this, patients were divided into two weight groups, those weighing $\leq$ 30 kg and those weighing > 30 kg, with patients receiving the aforementioned dosing that was rounded off such that the final target doses received are presented in the following table below. Doses greater than 5 mg were given in two divided doses:

Table 1. Dosing Table

Target Dose (Total Daily Dose) [a]	**≤30 kg Body Weight**	**>30 kg Body Weight**
Low Dose	5 mg daily	10 mg daily
Medium Dose	10 mg daily	20 mg daily
High Dose	20 mg daily	40 mg daily

[a] Doses above 5 mg/day were administered in two divided doses

Patients were allowed a single back titration by 5 mg of drug or placebo if intolerance was observed. Limited rescue medications were permitted. Data was collected in the form of a seizure diary. In order to be randomized, patients were required to have had at least one generalized seizure over the past 6 months and 2 drop seizures per week during the baseline observation period. Patients were 2 to 60 years of age. All patients must have been on a stable dose of 1 to 3 AEDs for at least 30 days prior to screening. Patients who were thought to have a progressive neurologic disorder were excluded.

The primary endpoint was the percent reduction in the weekly average frequency of drop seizures from the 4 week baseline to the 12 week maintenance period. Important secondary

endpoints included: 1) a comparison of the percent reduction in seizures from baseline to the first, middle and last 4 weeks of maintenance, 2) the percent change in non-drop seizures, 3) the use of rescue medicine. Other secondary endpoints were examined including both Physician and Parent/Caregiver Global Evaluation. There was no specific imputation for missing data; the days where such data were missing were simply not included in frequency calculation.

The primary analysis set was the modified intent-to-treat population, which consisted of patients with baseline data who had received at least 1 dose of medication and had at least one maintenance period measurement. Analysis was based upon a last observation carried forward. An ANCOVA was used with p value requirement for significance of ≤ 0.01. This is more stringent than the p value of 0.05 usually used, but may be justified based upon the Sponsor's presumption that they are providing us with one pivotal study and supportive data (study OV-1002, see below). The analysis was performed on a model with percent reduction in drop seizures as the dependent variable and treatment, pooled center, and baseline drop seizure rate as the independent variables. A step down hierarchical analysis, starting at the high dose, corrected for multiple comparisons.

A total of 238 subjects were randomized, with 59, 58, 62 and 59 patients in the placebo, low-dose, medium-dose and high-dose groups, respectively. Drop outs were generally similar across groups, with approximately 20 % in all groups, with the exception of the low dose group where drop-outs were approximately 9%. The reasons for dropping out varied between groups with discontinuation due to lack of efficacy being highest in placebo and low doses and those due to adverse effects being highest in the medium and high dose groups. Demographic variables were generally well matched between treatment groups. The baseline drop seizure rate was, however, 30 to 50 percent lower in the medium-dose group than that in the other groups. Approximately 70% patients were from the US. There were more males than females. Patients tended to be young with a mean age of 9 years old.

Results of the primary endpoint results are presented in the figure below (transcribed from the statistical review). An apparent dose-dependent change can be observed with the median and high dose being statistically significant to the preset criteria of 0.01. The low dose is significantly different, based upon the non-protocol driven criteria of $p \leq 0.05$.

Table 2. OV-1012 Primary Endpoint Analysis: Maintenance Period Percent Change from Basline in Drop Seizures

	Study OV-1012			
		Clobazam Dose Level		
Variable Statistic	Placebo N = 57	Low N = 53	Medium N = 58	High N = 49
Baseline drop seizure rate				
Mean (SD)	97.8 (170.7)	99.6 (206.0)	60.5 (122.5)	105.2 (163.3)
Median	35.5	29.2	22.5	46.4
Range	2, 920	2, 1077	2, 798	2, 856
Percent reduction during the maintenance period[1]				
Mean (SD)	12.5 (72.7)	41.6 (46.8)	47.8 (62.0)	69.5 (39.7)
Median	23.2	46.7	57.9	86.5
Range	-374, 100	-119, 100	-262, 100	-39, 100
p-value: comparison to placebo [2]		0.0120	0.0015	< 0.0001

Source: Study Reports

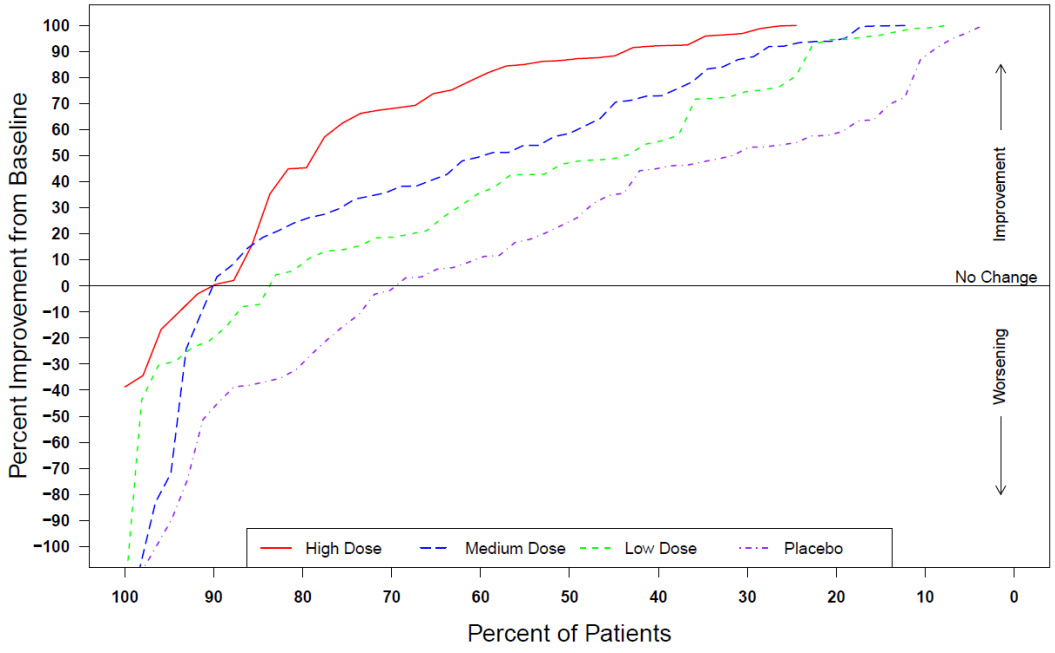
[1] Duration of the maintenance period was 4 weeks in Study OV-1002 and 12 weeks in Study OV-1012.

[2] In Study OV-1012, 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, and baseline seizure rate included as effects in the model.

The primary endpoint exhibited similar statistical significance results when it was analyzed through the non-parametric Wilcoxon rank-sum test. A variety of sensitivity analyses also confirmed these results including one that imputed baseline seizure rates for patients who discontinued, one that adjusted for numerous factors including baseline seizure rate and one that eliminated 7 subjects from a site where there was potential premature unblinding.

Of note, a cumulative distribution function (CDF) of the primary endpoint supported the dose dependency observed with all three doses. The CDF is presented in the figure below (transcribed from the Statistics review). A negative percent improvement represents seizure worsening over baseline.

Figure 1 Cumulative Distribution Function for Percent Reduction in Seizures in Study OV-1012



The FDA statistics reviewer, Dr Siddiqui, performed his own analysis of the primary endpoint and supportive data and found results consistent with those of the Sponsor's.

Examination of non-drop seizures revealed a nominal reduction in non-drop seizures in all dose groups as compared to placebo, but this change was only statistically significant in the higher dose group, and only based upon a nonparametric post-hoc analysis. When all seizures (drop and non-drop) were grouped, statistical significance mirrored that which was seen for drop seizures alone. Physician Rated Global Evaluation was statistically significantly improved in all dose groups while the Patient Rated Global Evaluation revealed statistically significant improvement in the medium and high dose groups alone. The description "statistical significance" of these secondary endpoints is based on a $p \leq 0.05$, although in many cases $p \leq 0.01$ criteria were met, and is not corrected for multiple comparisons.

Examination of tolerance was a particularly important secondary endpoint. This was analyzed by comparing the percent of patients achieving a $\geq 50\%$ reduction in average weekly rate of drop seizures from baseline to the first 4 weeks of the maintenance period who then experienced a return to baseline seizure during the last 4 weeks of the maintenance period or discontinuation due to a lack of efficacy. The percent of patients fulfilling this criterion were then compared amongst groups. According to this analysis, 5.3% to 9.5% of patients in the different drug treatment groups fulfilled the definition of tolerance as compared to 5.6% patients in the placebo groups. An additional analysis of tolerance based on responder analyses showed that the percent of CLB subjects with no change or improvement from the first 4 weeks to the last 4 weeks of the maintenance period in Study OV-1012 was greater than the percent of CLB subjects who worsened or withdrew in each treatment group. Dr Sheridan believes that these data are sufficient to support a conclusion of no obvious significant

tolerance over the studied period. I believe that there may be two problems with the first analysis to allow the conclusion of no tolerance: 1) the Sponsor is limiting themselves to selecting only patients who responded with a 50% or greater reduction in seizures during the first 4 weeks, 2) the Sponsor's criteria for a complete return to baseline during the last 4 weeks to define tolerance seems far too strict. Furthermore, this analysis does not provide a simple quantitative measure of tolerance. An analysis that the Sponsor performed to evaluate for missing data, however, partially addresses this issue. The Sponsor compared the percent reduction for patients in the first and last 4 weeks of the maintenance period to the baseline and no pertinent decrement was observed. This, of course, may be subject to the effect of dropouts, which was about was about 6 to 20% in different groups. However, this analysis was supportive of minimal or no tolerance. To further explore tolerance, the Sponsor was asked to perform a primary endpoint last observation carried forward analysis of the modified intent-to-treat set, comparing the percent reduction seizure frequency from baseline to the first 4 week and to the last 4 weeks. In this analysis, patients who dropped out before the last 4 weeks had their last 4 weeks carried forward. This analysis is presented in the table below as a difference from placebo. Although there was a mild desensitization effect in the low dose, none were appreciated in the higher doses. Dr Sheridan also points out that benzodiazepine tolerance is usually observed within the time period studied. In that case, the present study should be adequate to demonstrate the phenomena. Moreover, an analysis of an extension open label study (OV-1004) for up to periods greater the one year suggested a persistence of therapeutic effect over the period studied. This latter data is limited as it is open label, not blinded, and patients were allowed other medication adjustments.

Table 3. Percent Reduction in Seizure Frequncy (Change from Basleine), as Compared to Placebo, during the first 4 and last 4 weeks of the Maintaince period --an LOCF analysis of the MITT Set

	Dose Level		
Interval of Maintenance Period	**Low (0.25 mg/kg) N = 53**	**Medium (0.5 mg/kg) N = 58**	**High (1.0 mg/kg) N = 49**
First 4 weeks of Maintenance (Weeks 4-7) Mean difference from placebo in the Percent Change in Seizure frequency from baseline	29.5	37.6	53.2
Last 4 weeks of Maintenance (Weeks 12-15) Mean difference from placebo in the Percent Change in Seizure frequency from baseline.	23.9	36.3	63.7

OV-1002

OV-1002 was considered by the Sponsor as a supportive and not pivotal study as it is not of typical design; i.e. the study is of short duration and uses an active low-dose control. It was designed as a "phase 2" multicenter, randomized, double-blind, high/low dose comparison, parallel-group study. The study compared two arms, low and high CLB dose, which are identical to those used in OV-1012. Titration and baseline were identical, but the maintenance period was only 4 weeks long. Primary endpoint (percent change in drop seizures) and its analysis was similar, except for the use of non-parametric testing. Many of the secondary endpoints were similar to the above study. A total of 68 patients were randomized.

Demographics were generally well matched between groups. Baseline seizure activity was somewhat higher in the high dose group. Only US patients were studied and there was a preponderance of Caucasians. Results of the primary endpoint analysis are presented in the table below (transcribed from the statistical review). The high-dose group exhibited statistically significant greater seizure control than did the low-dose group. Secondary endpoints were similarly affected as they were in study OV-1012. In particular, there was a significant reduction in non-drop seizures when comparing the high to low dose. An analysis by the Dr. Siddiqui, the statistical reviewer, confirmed the Sponsor's analysis.

Table 4. OV-1002 Primary Endpoint Analysis: Maintenance Period Percent Change form Baseline in Drop Seizures

	Study OV-1002	
	Clobazam Dose Level	
Variable Statistic	Low N = 29	High N = 32
Baseline drop seizure rate Mean (SD) Median Range	 142.0 (190.2) 66 5, 661	 209.1 (229.2) 97 8, 924
Percent reduction during the maintenance period[1] Mean (SD) Median Range	 10.1 (122.3) 29 -531, 100	 85.2 (17.1) 93 48, 100
p-value: comparison between high and low dose [2]		< 0.0001

Source: Study Reports
[1] Duration of the maintenance period was 4 weeks in Study OV-1002 and 12 weeks in Study OV-1012. Treatment, pooled center, and baseline seizure rate included as effects in the model.
[2] In Study OV-1002, p-value for treatment difference (high versus low dose) from 1-sided Wilcoxon rank-sum test.

Dr Sheridan notes that although this study is considered supportive, it provides very strong evidence for efficacy. Its principal limitations were its inability to examine habituation because of its short duration and lack of a complete examination of the dose response relationship. This, however, was examined in study OV-1012 and is also supported by open label data.

Subgroup Analysis

A subgroup analysis of study OV-1012 by the Sponsor and statistical reviewer suggested that the therapeutic effect is independent of ethnicity (Asian/Caucasian), sex, and country of origin at all doses. Age did not appear to be a factor except for absence of a therapeutic effect observed in the adolescent age group. As noted by Dr Siddiqui, this is likely a sampling error, considering the small sample examined. I agree.

Conclusions

Both the clinical and statistical reviews agree with the Sponsor's conclusion for the proof of efficacy and the maintenance of effect over the period of time studied. While study OV-1002 was considered as supportive, except for the issues noted above, it can be considered a second pivotal type study. The robust statistical results (low observed p value) in study OV-1012 is also highly supportive of a conclusion of efficacy. There was also adequate evidence that no substantial tolerance was observed at the studied doses.

The issue remaining is what should be the recommended doses. Dr Sheridan notes that while the low dose did not achieve the predetermined statistical significance, it did achieve statistical significance based upon a lower, but more widely used standard of $p < 0.050$. Moreover, there was a positive dose response relationship throughout this period. (b) (4) In discussions of the review team, a decision was made to recommend the full range of doses. This will be done by providing the dosing titration schedule from the low to the high doses used in the study and by recommending that titration proceed based upon the clinical response (tolerance) to the drug. This strategy is generally used in clinical practice. I agree with this.

8. Safety

The safety review was performed by the Dr. Gerry Boehm, with the supervisory review performed by Dr. Sally Yasuda.

The safety data was derived from 56 trials with a total of 2,236 exposed patients as well as from postmarketing experience in countries were CLB has been approved. The core safety data included studies performed by the Sponsor from 8 Phase I trials and the above described 3 Phase 2/3 LGS trials (2 controlled and 1 open label studies), and includes a total of 633 individuals. The remainder 1603 subjects were from 44 older "Legacy" trials performed 2 to 4 decades ago by other sponsors. Source data was not available for the Legacy studies, and as per Dr. Boehm, the Sponsor submitted these "for completeness." Most Legacy reports studied patients with psychiatric disorders; one study (#301) included children (6 months to 17 years) with epilepsy (n=119), including patients with partial and secondary generalized as well as primary generalized tonic-clonic seizures. Exposure duration could not be fully reconstructed from the Legacy trials because incomplete accounting. But, at least a third of patients were exposed to doses as great or greater than those which are being recommended for LGS patients as a result of the pivotal trials.

The Sponsor notes that, out of the total of 633 subjects in the core safety database, 253 subjects were exposed to CLB for at least 6 months and 197 subjects were exposed for at least 12 months. Dr Boehm notes that the doses included in these exposures were in the ranges proposed by the Sponsor in their recommended labeling. Although total exposure fulfills ICH guidelines, the 6 and 12 month exposures do not. As noted by Dr Boehm, these data are supplemented by the Legacy reports along with postmarketing experience. Considering these

factors and the orphan status of the disease, Dr Boehm and Dr Yasuda believe the exposures are adequate.

Deaths

A total of 9 deaths were reported associated with CLB treatment in the core LGS safety database, all of which occurred in the open label extension trial, OV-1004. Two additional deaths were reported in the control groups in the Legacy studies. The age of patients who died in the core database were 4 years to 36 years old, 6 of whom were ≤12 years of age. The cause of death was as follows: pneumonia in 4 patients, unidentified cause in 3 patients, seizures followed by "respiratory failure" in 1 patient, "leg hematoma" and sepsis in 1 patient. Dr Boehm notes that, whereas 5 deaths were respiratory in nature (4 with a mention of pneumonia), it was difficult to relate the deaths directly to medication as these patients had severe underlying neurologic disability with documented aspirations, gastro-esophageal reflux and other pneumonia risks, such as serious neurologic disabilities. Pneumonia is not an uncommon cause of morbidity and death in patients with seizures, particularly with a serious syndrome such as LGS. I believe these pneumonia data are difficult to interpret because they are all derived from the open label phase, without a comparator. Additionally, as pointed out by Dr Boehm, they occur in the background of co-morbid risks (but see below). Dr Yasuda also agrees with this

Serious Adverse Events

No serious adverse events (SAEs) were observed in the core database in the Sponsor's phase 1 trial.

Of the Sponsor's phase 2/3 open label/control studies, SAEs were reported 103 of 300 patients. My accounting of the tables provided by Dr Boehm of this data reveals that the largest grouping of the SAEs can be classified into one of three catagories:1) pneumonia related (pneumonia, pneumonia/aspiration/ lobar pneumonia and pneumonia/viral), n=45, 2) epilepsy-related events (LGS, status, grand mal, convulsions, epilepsy, myoclonic epilepsy), n=36, and 3) respiratory related events (sleep apnea, respiratory distress, aspiration hypoxia and respiratory failure), n=14. Epilepsy-related events are not unexpected in this data base. More discussion of pneumonia and the respiratory events are contained below in the section on Issues of Interest under the title of Pneumonia.

Other SAEs of interest in the phase 2/3 studies included the following:

- Three cases of thrombocytopenia were reported. All cases were confounded. Thus, one case exhibited resolution with the temporary holding of valproic acid and CLB; valproic acid is labeled for thrombocytopenia. Another case exhibited an exacerbating

and remitting course in a patient on multiple drugs. In the third case, platelets were low at baseline, before CLB was initiated, and resolved when both valproic acid and CLB was discontinued. Dr Boehm and Yasuda believe these cases to be confounded, and I agree.

- Two cases of pancreatitis were noted. Both were thought by Drs. Boehm and Yasuda to be confounded and potentially a result of concomitant valproic acid. I agree with this conclusion. One resolved despite the continuation of the CLB.
- There was one case of renal tubular necrosis associated with septic shock. As this resolved despite the continuation of CLB, it is unlikely to have resulted from CLB.

No patients were identified in the Legacy reports as having "serious adverse event," as this categorization was not required at the time that such studies were reported. The Sponsor therefore attempted to perfom their own post-hoc categorization. This reporting issue probably, in part, accounts for the small number of identified cases. Only 5 patients were identified in the psychiatric Legacy studies and these consisted of worsening underlying psychiatric disease, appendicitis, "reason unknown", and jaundice. The latter case would be of interest; however, it was identified as related to alcohol cirrhosis and is also discussed in the section on laboratories. Twelve of 119 patients were identified with serious outcomes in the epilepsy Legacy trial. No definitive pattern appears in these cases. They do not shed additional light above and beyond the present phase 2/3 database.

Dropouts

Of 333 patients studied in phase 1 trial, 13 were noted to discontinue because of adverse events (AEs). Discontinuations involving more than one patient included 3 for increase in transaminase, 3 for somnolence and 2 for dizziness. The transaminase increases were moderate in nature, did not include bilirubin changes and reversed on drug discontinuation. More discussion of transaminase elevations can be found below in the section on Laboratory Changes.

Forty-four (16%) of patients participating in the phase 2/3 LGS discontinued because of AEs. In general the accounting for all discontinuations appeared to follow a dose-dependent relation. For example, in study OV-1012, drop-outs from AEs were 3.4%, 6.9, 12.9% and 22% in placebo, low-dose, medium-dose and high-dose groups, respectively. AEs leading to discontinuation in one or more patients included somnolence (n=7), aggression (n=6), lethargy (n=5), ataxia (n=4), pneumonia (n=3), death (n=2), fatigue (n=2), insomnia (n=2), restlessness (n=2), and urinary incontinence (n=2). Upon examination of Dr Boehm's list of other reported reasons for discontinuations in single patients, many appear to fall in the neuro/psychiatric category and include gait disturbance, irritability, hypophagia, chorea, cognitive disorder, hypotonic, motor dysfunction, sedation, abnormal behavior, listlessness, negativism and perseveration. In general, many of the neuro/psychiatric events exhibit greater rates of discontinuations at higher doses (e.g. ataxia, fatigue and somnolence). Dr Boehm believes that the data is too sparse to allow a definitive conclusion of dose response, but I believe that there is some suggestion of a dose response, which is particularly suggested when grouping the

neuro/psychiatric events together. This is further supported by the common adverse event data described below and what is known from the benzodiazepines as a class.

There was one case of discontinuation associated with a rash that was initially described as a "febrile exanthema" but later thought to represent DRESS syndrome. This is discussed in further detail in the section on Issues of Interest.

The Legacy studies appeared to confirm the above with discontinuations greater in drug than placebo groups, most notably for neuro/psychiatric events (e.g. somnolence, confusional state, asthenia fatigue and irritability). Although other reasons for discontinuation (e.g. urticaria, infections vomiting) were noted; no pattern of other notable organ system involvement was gleaned.

Common Adverse Events

Of the LGS phase 2/3 open and controlled study database, the most commonly reported AEs were somnolence (25%), upper respiratory infection (24%), pyrexia (19%), pneumonia (15%), lethargy (14%), nasopharyngitis (14%), constipation (14%), aggression (13%), fall (13%), otitis media (13%), insomnia (12%), urinary tract infection (11%), drooling (11%), sedation (10%), skin laceration (10%), convulsions (9%) and viral infection (9%).

A special analysis was performed to examine the temporal features of somnolence. This analysis demonstrated that somnolence tended to occur during titration and to resolve with continuing treatment.

Dr. Boehm performed an evaluation of AEs in study OV-1012 similar to one performed by the Sponsor, identifying those AEs more common in any dose group and with an incidence that is $\geq$ 5%. These data are presented in the table below (reproduced from the FDA revised Sponsor's table to be included in the label). The most common adverse event treatment effect when examining all combined dose groups (% drug- % placebo) were somnolence-related events, pyrexia, drooling, constipation and cough, with treatment effects of 13 %, 10%, 6%, 5% and 5%, respectively. There was a preponderance of neuropsychiatric events (e.g. somnolence, ataxia etc.) and upper respiratory events (e.g. cough, bronchitis, and pneumonia).

Table 5. Common Adverse Reactions Events

System Organ Class Preferred Term	Dose Level				All Clobazam N=179 %
	Placebo N=59 %	Low[a] N=58 %	Medium[b] N=62 %	High[c] N=59 %	
Gastrointestinal Disorders					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
General Disorders and Administration Site Conditions					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
Infections and Infestations					
Upper respiratory tract infection	10	10	13	14	12
Pneumonia[d]	2	3	3	7	4
Urinary tract infection	0	2	5	5	4
Bronchitis	0	2	0	5	2
Metabolism and Nutrition Disorders					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
Nervous System Disorders					
Somnolence-related events[e]	22	28	32	44	35
Drooling	3	0	13	14	9
Ataxia	3	3	2	10	5
Sedation	3	2	3	9	5
Psychomotor hyperactivity	3	3	3	5	4
Dysarthria	0	2	2	5	3
Psychiatric Disorders					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
Respiratory Disorders					
Cough	0	3	5	7	5

[a] Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight

[b] Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight

[c] Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

[d] Includes the adverse events pneumonia, lobar pneumonia, and bronchopneumonia

[e] Includes the adverse events somnolence, sedation, lethargy, hypersomnia, and depressed level of consciousness

The phase 1 and Legacy reports suggested a similar profile of adverse events except for a suggestion of syncope associated with both CLB and diazepam.

When examining AEs in the control phase 2/3 trials on LGS as a group, dose dependency was not obvious, although there was a suggestion of this when looking at discontinuations from AEs (see above). The phase 2/3 control studies suggested a dose response relation in two AEs, constipation and somnolence. The formal QT study (OV-1022), however examined substantially higher doses than those used in the efficacy studies (i.e. 20- and 80-mg BID vs 5- to 20-mg BID). These data did provide further evidence for a dose-response relationship for somnolence and suggested additional evidence for a dose-response relationship of other AEs, most notably dizziness, dysarthria and gait disturbance.

The Sponsor attempted to examine the role of demographic variables (age, race, geographical region) in AE incidence. As noted by Dr Boehm, this data was difficult to interpret because of the lack of information on background norms and the small size of the controlled trials.

Other

Dr Boehm also examined the adverse event database for events associated with blood dyscrasias, hepatotoxicity and serious rash. Some of these issues are described elsewhere in this review. The conclusion, however, is a lack of data to implicate CLB as a causal agent of any of these events. There were two cases of pancreatitis, previously discussed, which were confounded.

Laboratory Changes

Dr. Boehm notes that laboratory analysis in the Legacy studies was not based upon today's standards. Thus, for the Legacy epilepsy study, only baseline laboratory tests were collected in all patients; follow-up labs were collected in those cases as "deemed necessary." Dr. Boehm notes these results "do not represent comparisons of randomized groups." In the controlled Legacy Psychiatry Trials from US and Canada, about half of the patients (approximately 100) had laboratory values recorded. This was lower in the non-US studies, with 10% of patients (approximately 38) having recorded laboratory values.

Examination of hematology results in the Phase 1 trials and Legacy reports could not identify a definitive signal. Although in the controlled phase 2/3 trials there was a slightly greater incidence in the decrease of RBC indices as compared to placebo (12% vs. 5%), the magnitude of this effect was small, and, as Dr. Boehm notes, is of "unknown clinical significance." There were no consistent changes in other indices. According to the Sponsor, Dr Boehm notes that 18 patients experienced a "blood dyscrasia" adverse event in the phase 2/3 database. Twelve were in the open label extension trial. Of all patients, 16 experienced low platelet counts, 1 had a low WBC count and 1 was reported with leucopenia. No such AEs were reported in other studies. As noted above, three of the cases, reported as thrombocytopenia were considered serious but confounded (see Serious Events). Dr Boehm notes that the non-serious

cases of thrombocytopenia were confounded by the use of concomitant suspect anticonvulsants. A number of reports of blood dyscrasias were also described in postmarketing reports, but Dr Boehm believed that attribution could not be determined because of confounding factors.

Examination of changes to blood chemistry did not reveal an obvious pattern of change, although some sporadic abnormalities were noted. Thus, although some cases of potentially clinically significant (PCS) increases in ALT and AST values were noted in the phase 1 studies, no consistent changes in these indices occurred in the controlled studies. There was a small preponderance of alkaline phosphatase PCS values in drug group as compared to placebo, which was also reflected in mean changes. The changes in alkaline phosphatase were not noted by Dr Boehm, but their significance, in the absence of consistent changes in transaminase or bilirubin, is uncertain.

Liver-related AEs were identified in the controlled trials, but no obvious signal could be gleaned. All were mild in nature. In the open label phase 3 trial, 9 liver-related AEs were identified; only one was classified as serious. Bilirubin was not elevated in this case and other confounding variables were identified. Three liver-related AEs, one of which was serious with elevation of bilirubin, were reported in the Legacy reports. The single serious event was likely a result of alcoholic cirrhosis (see Serious Adverse Events above). Bilirubin was not reported elevated in the other cases and elevation of transaminase was not dramatic. While postmarketing cases of liver hepatotoxicity have been reported, causality was not obvious. Dr. Boehm notes that a PubMed search could not identify a risk of hepatotoxicity with CLB specifically or with benzodiazepines in general. Dr Boehm concluded that this data does not suggest an hepatotoxic effect.

Shift tables alone revealed higher calcium, sodium and triglycerides, but in the absence of significant PCS and mean changes. Legacy reports failed to add additional information.

Dr Boehm found no obvious signal in data on urinalysis.

Vital sign data were available from the formal QT study (OV-1022) and the phase 1 and 2/3 studies. While sporadic PCS values were reported in pulse and blood pressure, such events were not associated with clinical symptoms and did not appear to be drug related. PCS values in the placebo control study did not convincingly indicate a drug-dependent effect based upon a placebo-drug group comparison.

EKGs recorded from study OV-1012 as well as those from OV-1022 did not reveal any significant changes.

The IRT team concluded no significant effect on the QT interval, based upon the formal QT study, OV-1022. The IRT team noted a positive moxifloxacin control, indicating adequate sensitivity. The IRT believed the exposures used in the study were sufficiently high to cover expected clinical scenarios. This lack of effect was observed notwithstanding non-clinical trial demonstration of binding of both CLB and N-CLB to the HERG channel.

Issues of Interest

Pneumonia

(b) (4)

Pneumonia is not an uncommon event in patients with LGS, or for that matter, with any serious seizure disorder.

Dr Boehm, noting this as a common disease related adverse event, further explored whether (b) (4)

First, he noted that Pneumonia was not reported in the psychiatric Legacy studies.

To explore causality (drug vs. disease), Dr. Boehm explored the association of pneumonia onset to either disease-related events or drug-related events. In this case, the presumption is that pneumonia may be aspiration-related either secondarily to drug-related somnolence and increased secretions, or secondarily to seizure-related aspiration. LGS-related pneumonia may have other causes (e.g. other drugs, neurologic impairment, or nutritional status). To explore this issue, Dr Boehm requested additional analyses from the Sponsor. Thus, an examination of the importance of a variety of covariates that may be related to pneumonia demonstrated that drooling/hyper-secretion and somnolence related AEs were not related to pneumonia onset, but that pneumonia was frequently preceded by seizures. I do not think this information is contributory to understanding causality. These results would be expected simply by the fact that, even with seizure treatment, seizures were far more commonly reported than were any of these adverse events. In a temporal analysis of pneumonia, Dr. Boehm believes that the observation that the risk of pneumonia was relatively constant for an extended period following the initiation of treatment supports the lack of causality; i.e. one would have expected the risk to be initially increased. I do not believe this is contributory as the only way to analyze such data is by a pre- and post-drug comparison. The pre-drug risk, however, is not available. Dr Boehm also looked at other labeled agents for LGS. The best information was gleaned from the data from the rufinamide label. In this case, a small control trial identified no cases of pneumonia in the placebo but 2/74 cases in the drug treatment group, and an incidence of 11/135 (8 %) cases in the phase 3 LGS database. Dr Boehm concluded that there was insufficient data to identify a casual relation. Of importance to his argument are the data described above and the fact that there is a strong risk in the LGS population of developing pneumonia.

I believe causality attribution for drug-related pneumonia is difficult, but I do believe that there may be adequate data for (b) (4) labeling. My argument for the is as follows

- Examination of pneumonia in study OV-1002 revealed 2/36 cases of non-serious pneumonia in the high dose group and none in the low dose group. In OV-1012, all pneumonia cases were reported as serious; 1/59 was observed in the placebo, 2/58 in the low dose, 2/62 in the medium dose and 4/59 in the high dose group. To me, this suggests a dose response relation in two separate studies.

- Somnolence and Drooling were relatively common adverse events and appeared to occur in a dose/response fashion.
- Bronchitis and cough were observed to be drug-related. Such events may be a further indication of the risk of aspiration.
- The incidence of pneumonia (15%) was very high in phase 2/3 LGS trials and greater than that associated with similar studies for rufinamide (8%). Albeit, such cross study comparisons are difficult particularly without knowing period of exposure.

Considering that many of the cases of pneumonia are considered serious, (b) (4) It will be included in the Adverse Reactions section, by its inclusion in the common adverse reactions table.

DRESS

There was one case of discontinuation associated with a rash that was initially believed to be a "febrile exanthema" but later thought to represent DRESS syndrome, as there was associated elevation in LFTs, a palpable spleen, mild anemia, granulocytopenia. There was no eosinophilia or lymphadenopathy. The Sponsor believed that this was not DRESS in a later review. In a review of the literature, Dr. Boehm could not identify any cases of DRESS associated with CLB and believes no labeling is necessary, but there should be post-vigilance. I would add that the above identified patient was on other agents (valproic acid) that are associated with multi-organ hypersensitivity. I agree with Dr Boehm's conclusion as does Dr. Yasuda.

SUDEP (Sudden Unexplained Death in Epilepsy)

Three cases in the seizure database were identified as potential SUDEP. The small sampling and common occurrence of SUDEP in the patients with LGS, or other serious seizure disorders, does not allow for a definitive conclusion on this drug's potential effect on SUDEP.

Carcinogenesis

Lundbeck identified few cancer-related AEs in the CLB safety databases. In the open label extension trial OV-1004, Lundbeck found the following 3 cancer AEs: benign breast neoplasm, skin papilloma, and osteochondroma (all benign). One subject from the Legacy epilepsy trial had a cancer AE. This patient had a low grade astrocytoma and underwent left temporal lobectomy. Lundbeck identified 11 postmarketing reports of patients diagnosed with malignancies. The Sponsor believed there was inadequate evidence for carcinogenesis because of wrong temporal relation or confounding factors. Dr Boehm identified the type of neoplasms, after having read individual postmarketing, reports: glioblastoma recurrence, promyelocytic leukemia, acute lymphocytic leukemia, acute leukemia (not further specified),

astrocytoma, mycosis fungoides (n=2), myelodysplastic syndrome, hepatic adenoma, and non Hodgkin's lymphoma.

Although no conclusions are specifically addressed in either Dr. Yasuda's or Dr. Boehm's review, I believe that the clinical and postmarketing reports are inconclusive. Reports are generally rare and involve different types of cancer with apparent confounding factors. For this reason, the best data would be obtained from animal studies. As described above, the provided animal data has a number of limitations, but at this point it does not indicate an obvious signal. Additional animal studies will be requested as part of a PMR.

Reproduction and Pregnancy Data

The Sponsor proposes Pregnancy class C. Dr. Boehm notes that the Sponsor recommends that CLB "should not be used in the first trimester of pregnancy and thereafter only if strictly indicated." Cases of congenital malformations were identified from postmarketing data. However, many of these cases appeared to be confounded by the presence of other drugs. Sporadic congenital malformations were also observed in case reports in the literature, which included those confounded by other, suspect agents. These data, in my opinion, are not adequate to definitively conclude causality. Of note, however, many benzodiazepines are labeled as class D.

Dr Gregory Dubitsky of DNDP performed a review on 5/7/96 in response to a citizen's petition for more strict pregnancy labeling for the use of benzodiazepines as a class of "sedative" agents, and concluded:

> "Although some human investigations have suggested a risk of malformations, the better studies indicate that any risk is likely to be small. Overall, human studies to date have not been adequate to provide a reliable estimate of teratogenic potential or neurodevelopmental effect; on the other hand, even the better studies have not reasonably ruled out risk."

Dr Dubitsky further notes that:

> "While an argument could be made that labeling is now too strong[1], given lack of a clear teratogenic effect in man, this position is based on the fact that such an effect has not been ruled out and the desirability to be conservative in dealing with an important safety issue."

(b) (4)

[redacted]

There were additional data in the application which indicated the potential for a variety of other problems resulting from the transfer of drug across the placenta and resulting infant pharmacologic toxicity at birth. This included changes in muscle tone, sedation, low APGAR

[1] Referring to the Class D.

scores, and even withdrawal syndromes. This is consistent with other benzodiazepines and has good biologic plausibility.

Suicidality

As Dr. Boehm notes, there were limited data on the risk of suicidality. Only 1 patient, in the Legacy study, was reported to have experienced suicidal ideation. The Warnings and Precautions section will contain anticonvulsant class labeling for suicidality.

Addiction and Withdrawal

CSS performed a review and notes that, based upon the provided non-clinical and clinical data, this drug is similar to other benzodiazepines and therefore should be scheduled as category IV of the CSA. The drug has the potential of producing physical and psychological dependence. Withdrawal symptoms have been reported ranging from minor (e.g. anxiety) to major (e.g. seizures, psychosis and hallucinations). These are included in the Warnings section of the label. The CSS reviewer also recommends labeling of potential increased exposure to drugs metabolized by CYP2D6, such as dextromethorphan. The drug should be withdrawn slowly. This information will be included in the (b) (4)

Conclusions

Both Drs. Boehm and Yasuda believe that none of these safety issues should preclude approval. I agree.

9. Advisory Committee Meeting

None.

10. Pediatrics

As an Orphan Drug, there are no PREA requirements. The majority of patients studied in this research program were less than 12 years old, with patients down to 2 years old included. This essentially covers the age range of at risk patients.

11. Other Relevant Regulatory Issues

Dr Sheridan examined financial disclosure issues for investigators involved in the phase 2/3 studies. The information appeared complete and in general he did not identify a conflict of interest. He did identify 5 Sponsors whom were awarded $25,000 to $75,000 for various

consultative works not involving CLB. To confirm that the data derived from these investigators did not influence the results, Dr. Siddiqui, the statistical reviewer, was asked to perfom a statistical analysis excluding patients from these sites (about 9 percent of all patients studied). This reanalysis did not significantly influence the final conclusions of efficacy.

DSI inspected 4 sites, 2 in each "pivotal trial." Three were domestic and 1 foreign (India). Regulatory violations were identified at 2 sites, but these were believed "not likely to critically impact primary efficacy and safety analyses."

12. Labeling

The label editing was performed by the group of FDA reviewers and the Sponsor has been consulted. The final label is included in the approval letter.

13. Recommendations/Risk Benefit Assessment

- *Recommended Regulatory Action:* Approval

- *Risk/Benefit Assessment:* The review team consensus was of a favorable benefit/risk ratio. Approval is recommended. The drug clearly showed efficacy, without obvious signs of tolerance to its therapeutic effect. While there were a number of risks noted, these did not outweigh the expected benefit.

- *Recommendation for Postmarketing Risk Management Activities:* No REMS were deemed to be necessary. There will be a non-REMS medication guide, as there are with all anticonvulsants. The predominant reason for this is to communicate the risk of suicidality to patients. But, the communication of other facts regarding this drug is considered helpful.

- *Recommendation for other Postmarketing Study Commitments*: Our non-clinical Pharmacology/Toxicology review team recommends PMRs to further explore carcinogenesis as well as teratogenesis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN HERSHKOWITZ
10/20/2011