CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	22-253, 22254, [redacted] b(4)
Submission Number	0
Letter Date	9/28/07
PDUFA Goal Date	10/28/08 (following extension)
Reviewer Name	Norman Hershkowitz, MD, PhD
Review Completion Date	10/28/08
Established Name	Lacosamide
(Proposed) Trade Name	Vimpat
Therapeutic Class	Anticonvulsant
Applicant	Schwarz Biosciences Inc. (UCB)
Priority Designation	S
Formulation	1) Tablets 50, 100 150, 200, 250 and 300 mg (22253) b(4) 2) iv solution (22254) [redacted] b(4)
Sponsor's Dosing Regimen	100, 200 [redacted] mg BID b(4)
Indication	Epilepsy of Partial Onset
Intended Population	Adjunctive Treatment >16 years

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b(5)

1 EXECUTIVE SUMMARY

The CDTL acted as the primary efficacy reviwer. Therefore, the CDTL review is being reprinted, in part, below so as to serve as the Executive summary.

Introduction

Lacosamide has been developed for two separate indications, partial onset seizures and pain associated with diabetic peripheral neuropathy (DPN). This CDTL Division of Neurology Prodcuts (DNP) review will concentrate on efficacy results in partial onset seizures. That for DPN will be reviewed by Division of Anesthesia, Analgesia and Rheumatologic Products (DAARP). Safety data in this application has been reviewed by both division, and while this review will concentrate on safety in epilepsy, all data will be discussed. Because of specific interest in a potential cardiac signal the Division of Cardiovascular and Renal Products (DCRP) was asked to comment not only on the formal QT study but issues of PR prolongation and general cardiac safety.

Background

According to the Sponsor Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a member of a series of functional amino acids. From a mechanistic perspective lacosamide appears to act as a sodium channel blocker, an action shared by a number other anticonvulsants including phenytoin, carbamazepine, oxcarbazepine and lamictal. The Sponsor also notes that lacosamide's anticonvulsant activity may also be related to its ability to bind to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. This reviwer believes that this latter mechanism is highly speculative.

Clinical/Statistical- Efficacy

The clinical efficacy review was performed by this CDTL, Dr. Norman Hershkowitz.

The Sponsor submitted 3 adequate and well controlled trials for review. Supportive studies were also included. The adequate well controlled trial consists of a phase 2b, dose finding study (SP667) and two phase 3 trials (SP754 and SP755). All three trials were of similar design (see below). The table below presents a summary of dose, time and numbers of patients studied in these protocols.

Trial number/Clinical development phase/Trial design	Number of subjects randomized to receive LCM[a]	Number of subjects randomized to receive placebo[a]	Maximum duration of treatment[b]
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97	21 weeks
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104	21 weeks
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163	18 weeks
Total	200mg/day: 270 400mg/day: 471 600mg/day: 203 Total: 944	364	

LCM=lacosamide

a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

b All 3 trials had a 12-week Maintenance Phase.

The Sponsor describes 4 additional trials as supportive for the claim of efficacy. All supportive trials were uncontrolled and open-label studies whose data principally contributed to the safety database.

As noted above all three studies were of a similar design. They were all multi-institutional, double-blind, placebo-control, parallel cohort, adjunctive treatment studies in adults (>16 years old) with partial epilepsy (simple partial, complex partial and partial secondarily generalized) Trials were rather similar in design. The schedule of evaluations was similar across studies.

Initial screening was performed on the first day of the baseline period. Seizure diaries were provided at this time and patients were instructed in their use. Patients then entered an 8 week baseline phase. They were randomized following this period if they continued to fulfill inclusion/exclusion criteria (there was a requirement for a minimal seizure frequency during this period). Inclusion/exclusion criteria were relatively routine for this class of study. Patients entered the treatment phase following randomization which consisted of a titration and a maintenance period. The titration period in SP 667 and SP754 were of 6 weeks duration and that of SP 755 were of 4 weeks in duration. All titrations proceeded at the rate of 100 mg qD (in a BID divided dose) every week. All doses were administered in an evenly divided BID regimen. Subjects who could not tolerate their final dose were permitted one back step of 100 mg/day during the titration period. The titration period was followed by a 12 week maintenance period in all studies. No back titration was permitted during this period. After the study was completed the patients were given a choice to continue on lacosamide in an open label study at a dose of 200 mg/day. If they so decided, they would undergo a blind transition period where they were titrated to a dose of 200 mg/day. If they declined they would undergo a down-titration that would proceed at a rate of 200 mg/day every week.

The primary endpoint required by the FDA and EMEA where different, but were based upon the standards typically used for those agencies. These different primary endpoints were agreed upon by the FDA in an end of phase 2 meeting. The FDA assigned endpoint was the change in partial seizure frequency per 28 days from baseline to the maintenance period. Seizure frequency (SF) was calculated by the formula: SF = (Number of Seizures) x (28 / D), where, D is the number of days. The manner that baseline seizure frequency was calculated was different between the initial dose ranging study, SP667 and the two phase 3 studies, SP754 and SP755. These differences were protocol driven. Thus, for SP667 baseline values were based upon the complete 8 week baseline period, but for SP754 and SP755 baseline value was based upon the last 56 days of the baseline period. For patients who discontinued during maintenance phase an LOCF frequency value was calculated. If the patient dropped out prior to entering the maintenance period an LOCF value for the titration period was calculated.

Statistical analysis of the seizure frequency change was performed on the log-transformed seizure frequency[1] based on an ANCOVA model with terms for treatment and pooled site. Log-transformed average seizure frequency during the Baseline Phase was used as the covariate. This maneuver is rather commonly used in these studies to normalize such data. The seizure frequency between treatment and placebo was compared using LS means. Percentage reduction over placebo was calculated by: 100 x (1 - exp[LSM Treatment – LSM Placebo]), where LSM is the least squares mean from the analysis. This analysis was previously described in the Sponsor's statistical analysis plans. The log transformation allows a normalization of data. Criteria for statistical significance were $P \leq 0.05$.

The primary outcome described above and its method of analysis is similar to those used for the approval of a number of drugs. The single difference is the fact that only the maintenance period as opposed to the full treatment (titration plus maintenance period) was used to calculate post-

1 Log transformation was based upon the formula ln(x+1), where x is equal to the seizure frequency.

treatment seizures. More commonly the titration and maintenance are included in this calculation. Off note, this analysis was performed as a secondary endpoint analysis.

A number of secondary analyses were preformed including, but not limited to: 50 percent responder to Maintenance Phases (the EMEA primary endpoint), change in partial seizure frequency per 28 days from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases: a more typical for the primary endpoint as noted above), other responder rates($\geq$75%, $\geq$50% and $\geq$25%), Proportion of seizure-free days during the Maintenance Phase for subjects who entered the Maintenance Phase, proportion of subjects who achieved "seizure-free status" during the Maintenance Phase for subjects who completed the Maintenance Phase, Response to treatment by seizure type, Clinical Global Impression of Change, Quality of Life in Epilepsy-31.

All 3 studies underwent changes in sample size during their implementation. One had a decrease in sample size because of unexpectedly fewer dropouts and 2 had an increase in sample size becasue a repeat calculation indicated that the original determination of standard deviation and effect size, based upon another anticonvulsant study, was incorrect. These changes were made without unblinding and, according to the statistics reviewer, Dr. Massie, are justified.

Drop out rate during the trial differed slightly between placebo and the 200 mg/day dose, with the ranges in trials being 11% to14% and 17 to 21% for placebo and lacosamide (200 mg/day), respectively. That for the 400 mg dose showed a larger difference with 11% to 14% versus 21 to 26% for placebo versus drug, respectively. High drop out rates where observed for the 600 mg/day with a range of 11 to 13% versus 33% to 42% for placebo and drug, respectively. Most drop outs in the drug treatment groups resulted from adverse events (see safety).

Subject demographics were comparable across treatment groups. The mean age amongst all studies was approximately 40 years old. Most patients were categorized as Caucasian with "black" making up only 2 to 6 percent of the studied population. Seizure types were also well distributed across treatment groups in all studies. Complex partial and partial secondary generalized were more common then simple partial seizures. The most common concomitant AED were carbamazepine (35.2% subjects), followed by lamotrigine (31.2%) and levetiracetam (29.0% subjects). The majority of patients were on 2 concomitant medications.

The results of the primary endpoint (percent change from baseline to maintenance) over placebo is presented for all three trials in the table below. The percent reduction from placebo is based upon logarithmically transformed data, but is actually very close to arithmetic percent changes. From these data it is apparent that both the 400 and 600 mg daily dose resulted in a significant reduction in seizures from placebo. This was also the conclusion of the Pharmaco-metrics reviewer, by Dr. Zhu, who noted that in a nonlinear regression least squares modeling response curve started to flatten out beyond the median exposure of 400 mg dose. From the data below, and as per Dr Zhu's analysis, there is no obvious additional therapeutic benefit observed for the 600 mg/day as compared to 400 mg/day. In the 2 studies that examined the 200 mg/day dose a therapeutic trend was noted. This effect, however, was statistically significant for only one study. This reviewer believes that the 200 mg dose is therapeutic in some patients but may on average have a smaller effect resulting in an inconsistent statistical finding between both studies.

Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	14.6%	0.1010	(-3.2, 29.4)
LCM 400mg/day (N=107)	28.4%	0.0023**	(11.3, 42.2)
LCM 600mg/day (N=105)	21.3%	0.0084**	(6.0, 34.1)
SP754			
LCM 400mg/day (N=201)	21.6%	0.0078**	(6.3, 34.5)
LCM 600mg/day (N=97)	24.6%	0.0061**	(7.8, 38.3)
SP755			
LCM 200mg/day (N=160)	14.4%	0.0223*	(2.2, 25.1)
LCM 400mg/day (N=158)	15.0%	0.0325*	(1.4, 26.8)

As noted above, the change in frequency from baseline to maintenance phase is not a typical endpoint. The more conventional endpoint of change from baseline to the experimental period (titration + maintenance) was examined as a secondary endpoint. Data from this analysis is presented below, and differs little from the primary endpoint. This serves as an excellent sensitivity analysis to the Sponsor's endpoint.

Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	10.8%	0.1650	(-4.9, 24.2)
LCM 400mg/day (N=107)	20.3%	0.0100*	(5.3, 32.9)
LCM 600mg/day (N=105)	21.3%	0.0033**	(7.8, 32.8)
SP754			
LCM 400mg/day (N=201)	19.0%	0.0043**	(6.4, 29.9)
LCM 600mg/day (N=97)	19.9%	0.0086**	(5.5, 32.1)
SP755			
LCM 200mg/day (N=160)	12.3%	0.0294*	(1.3, 22.1)
LCM 400mg/day (N=158)	15.1%	0.0164*	(3.0, 25.7)

The statistical significance of secondary endpoint, 50% responder rate (the EMEA primary analysis), exhibited results identical, in terms of which doses were statically significant from placebo, to the primary endpoints in the FDA analysis. Other secondary endpoints, dealing with numerical alterations is seizure rates exhibited statistical significant effects as compared to placebo or trended in the correct direction. The Global evaluations trended toward improvement in the 400 and 600mg doses. Effects of quality of life measures were small and inconsistent.

Another secondary endpoint was the reduction in seizures by seizure type (i.e. simple partial, complex partial and partial secondarily generalized). These data were only presented using descriptive statistics. There was likely insufficient power to draw definitive conclusions. In general both complex partial seizures and partial secondarily generalized all trended in a direction that suggested a therapeutic effect. The effect on simple partial was more inconsistent. No definitive trend was observed, with some studies showing decreases and others increases in seizure activity of drug over placebo. Nothing can be definitively drawn from these data as these seizures were the least frequently observed and the data would be prone to a sampling error.

Dr Massie, the statistical reviewer, confirmed the Sponsor's analysis for all performed studies. Dr Massie also noted that "overall, there was no compelling evidence that the treatment effect varied by gender." He also determined that there was no obvious age dependency for the age range studied (16 to 71 years of age). Considering the limitation of the small size of the non-Caucasian sample size, it was concluded that no obvious racial differences in effect was observed.

This reviwer concludes that both the 200, 400 mg/day dose (divided bid) impart a therapeutic effect in adjunctive treatment of partial seizures. The 600mg/day dose does not appear, on average, to be superior to the 400 mg dose. The 200 mg dose may, on average, appears to have a smaller therapeutic benefit. However, on an individual basis, dosing will have to be adjusted not only based upon therapeutic benefit but also on tolerability. As will be discussed in the safety section, the 600 mg dose was poorly tolerated.

The Sponsor intends to market — formulations of lacosamide: tablets, intravenous solution — . All pivotal studies were performed using a tablet formulation. Conclusions for efficacy for other formulations are based upon studies demonstrating equivalent bioavailability between those formulations and the tablet formulation. — . Bioequivalence was also demonstrated with the iv infusion solution when such infusions were performed over 30 and 60 minutes. Shorter infusions resulted in higher Cmax values in the formal bioequivalence studies (see Pharmacokinetic section above). b(4)

Safety

Two separate major safety reviews were perfomed because of the two independent proposed indications: one by Dr. Villalba, for its anticonvulsant indication, and the other by Dr Pokrovnichka, for the neuropathic pain indication. In addition cardiology was consulted, not to only comment on QT studies, but also on other cardiac issues described below. A CSS review is also included with scheduling recommendations (see below). Although the Sponsor has simultaneously submitted an application to the European Union for approval, there is no foreign marketing experience.

Dr Villalba principally reviewed phase 1 to phase 3 studies relevant for the epilepsy indication. Dr Vilalba also reviewed safety data from the studies using [redacted] iv as well as the tablet formualtions. Dr Pokrovnichka's review concentrated on the tablet as it applied to the indication for diabetic neuropathic pain (DNP). The application includes a total of 4012 unique adult subjects exposed to LCM (including all routes of administration, all indications and healthy volunteers). Of these, 1338 subjects were in the partial-onset seizure studies (1327 subjects from studies with the oral tablet) and 2001 subjects in the neuropathic pain studies. The exposures in the epilepsy studies where of sufficient dosage and duration and met ICH guidelines. The database included both double-blinded placebo-controlled and open label studies. Of the subjects with partial-onset seizures exposed to oral LCM, 199 subjects also received IV LCM in Phase 2/3 trials. Intravenous studies were generally shorter in duration and either open label or were designed for comparison to the tablet formulation. Assuming similar PK and no obvious local issues of irritation, while these studies use a much smaller database, they should be considered sufficient for a determination of additional risks over the oral formulations.

b(4)

In her review, Dr. Villalba distinguishes two phase 2/3 safety pools: EP S1 which includes patients from *all 3 placebo-controlled, double-blinded* studies and EP S2 which included all patients receiving drug product in *all* phase 2/3 studies. These will be referred to below.

Deaths

No deaths were observed in phase 1 trials. A total of 9 deaths were observed in the epilepsy phase 2/3 studies. Eight of these nine occurred during open label studies. No deaths were observed in the placebo group. This leaves a comparison of 1 in drug Vs 0 in placebo in the EP S1 population. It should be remembered that the placebo population was third the size of those who received drug in the EP S1 population. These numbers are insufficient to draw any conclusions regarding an excess of drug-induced deaths. Four deaths were believed to be result of Sudden Unexpected Death in Epilepsy (SUDEP). Calculations by Dr. Villalba revealed no excess over that which would be expected in the studied population. On death, in a patient with a history of depression, was attributed to a completed suicide. None of the other deaths followed a particular pattern that can be easily attributed to a common cause.

There were a total of 15 deaths in patients on lacosamide in the DNP population. Four of these (4/1023) were in the controlled studies with none (0/291) in the placebo group. Of the 15 total deaths a majority (8) were cardiac-related (ventricular fibrillation, myocardial infarction, heart failure (n=2), myocarditis, cardiac arrest (n=2) and sudden death). Such a number is not unexpected for a patient population with diabetes and with many patients also having a history of hypertension, coronary artery disease, cerebrovascular disease, and/or peripheral vascular disease. One of the cardiac deaths was noted to include myocarditis/toxic hepatitis which occurred following completion of LCM treatment. This case may represent a suspected case of multiorgan hypersensitivity and will be discussed below. Three of the cardiac deaths however were observed in the placebo control studies, which may be suggestive of a potential cardiac related signal. However, the numbers of patients exposed in the placebo population is substantially lower then that in the drug population. These data however must be viewed against the background of other cardiac events, which will be discussed below. All but two of the remainder of deaths (5) was from a variety of cancers. No one type stood out. One case of a completed suicide was observed. Suicide and suicide ideation will be discussed below.

Other Serious Adverse Events

Comparison by Dr Villalba of rates of serious adverse events in the EP S1 epilepsy population revealed a higher rate amongst patients on drug then on placebo: :i.e. 6.5% and 3.8%, respectively. No obvious dose response was observed for these grouped rates. The most frequent reported serious adverse events, classified by system organ class (SOC), were Nervous Systems Disorders (1.6% in placebo and 2.1% in lacosamide in the EP S1 pool). The most frequent single preferred term was "convulsions" with O.8 in placebo and 0.8 in the lacosamide group. While it may be unexpected that these rates are the same, when you lump all other epilepsy preferred terms (e.g. epilepsy, complex partial seizures, etc) you observe a comparison of 1.7% Vs 1.3%, in placebo and drug. Other, non-convulsive serious CNS adverse events observed which were more common in drug as compared to placebo groups, were dizziness, nystagmus, coordination abnormal, loss of consciousness and tremor. No placebo patients exhibited these vents. Except for dizziness and nystagmus which were observed in 0.3% and 0.2% of patients, respectively, all events occurred in only 0.1% of patients (1 patients). Although the numbers of some of these events are low, many of these events are common with other anticonvulsants, with CNS adverse events limiting the dose that can be used. These are very common adverse events reactions associated with this class of anticonvulsants.

The next most frequent SAEs in the EP S1 population for patients with epilepsy were in the Psychiatric disorders SOC (0.7% for LCM and 0 for placebo-treated patients). Psychiatric events included preferred terms such as hallucinations, epileptic psychosis, psychotic disorders, completed suicide (see above), suicide attempt and insomnia. As Dr Villalba points out, the risk of such events are commonly seen in patients with epilepsy and although occurred in small numbers were only observed in patients receiving lacosamide. Dr. Villalba consequently reviewed each case, many of which an alternative explanation could be found (e.g. previous history of similar behavior). Dr Villalba suggested that the low numbers and perhaps other explainable cases undermine a casual attribution to drug use. This CDTL agrees.

The next most common SAEs in the EP S1 population for patients with epilepsy included GI disorders systems (0.6% for LCM and 0.3% for placebo-treated patients, respectively) and infections (0.5% for LCM and 0.3% for placebo-treated patients, respectively). These events were not thought to be related to treatment.

Examination of SAEs in the EP S2 pool for the epilepsy population did not reveal much additional information. A high number of injuries from fracture were noted (16 patients) and were possibly thought to be related to dizziness and ataxia, which appear to be drug related.

Serious adverse events in the DPN controlled population were similar to that reported for the epilepsy population: i.e. 6.6% (68/1023) of subjects who received lacosamide and 4.8% (14/291) of subjects who received placebo. The highest rate in the controlled database, by SOC, of serous adverse events was under the classification of cardiac disorders. There was actually a greater percent rate in placebo then in the lacosamide group (1.7% vs. 1.3%, respectively). As noted in Dr. Yasuda's, safety team leader's review, most of the cardiac conduction/rhythm abnormalities (atrial fibrillation, atrial flutter bradycardia, tachycardia etc) recorded as SAEs were reported from subjects treated with lacosamide. Serious cardiac events in the placebo group included conduction abnormities limited to bundle branch clock but also experienced ischemia and failure. Nonetheless, it is difficult to conclude anything from this particular data in that such a population would be prone to cardiac problems and the numbers in the placebo group are rather small. As expected, and consistent with epilepsy data, the second most common SOC adverse events are under the rubric of "Nervous System Disorders" with 0.7% vs. 1.0% in placebo and lacosamide groups, respectively. There is, however, only a marginally greater rate in the lacosamide group. The common Nervous System Events included loss of consciousness, dizziness and balance disorder. This reviwer believes that generally loss of consciousness should be considered cardiac in origin unless there are positive neurologic findings. The Sponsor's categorization as neurological appears to be based upon the absence of evidence of cause, both cardiac and neurologic. This event may be better categorized as cardiac in origin. Two patients in the controlled studies who experienced loss of consciousness as a serious event in the controlled studies were in the lacosamide treatment group, no patients were in the placebo group. A complete analysis of syncope will be discussed in greater detail below.

One serious cardiac event was noted in iv studies. Thus a 48 year old male suffered bradycardia, with heart rates down to 26 bpm, (BP 100/60) 7 minutes into infusion of 150 mg over a 15 minute period. This patient was on a beta blocker for hypertension. The patient had previously taken this dose orally with no problems. Two cardiologists, consulted by the Sponsor, evaluated the case and diagnosed it as either bradycardia with functional escape, or AV block with sinus exit block. There apparently was problematic movement artifact. Dr. Stephen Grant, the FDA cardiologist who evaluated this case, believes it is likely a vasovagal reaction. Drs Villalba and Yasuda believe that a relationship between the infusion of the drug and the profound bradycardia is biologically plausible This reviwer agrees with the latter conclusion, but would also add that this was rapid infusion (15 min), as compared to the other tested rates (30 and 60 min), which resulted in somewhat higher concentrations (see Clinical Pharmacology). This, along with PK

studies, indicates to this reviwer that rates of 30 and 60, ——— minutes should be the labeled. b(4)

One last serious case that is of interest is a single case of hepatitis associated with nephritis that occurred 12 days after final exposure. LFTs achieved levels of 10 to 30 times the upper limits of normal and proteinurea was noted. No bilirubin was documented at the time of the event. Viral causes of hepatitis were ruled out. Both Dr Villalba and Yasuda believe that considering the multiple organ involvement this may represent a multiorgan hypersensitivity seen with other anticonvulsants (see below).

Discontinuations

A very obvious dose dependent discontinuation rate was observed for discontinuations resulting from adverse events in the EP S1 pool with 8.2%, 10.7%, 17.1%, and 34.7% such discontinuations in the placebo, LCM 200mg/day, LCM 400mg/day, and LCM 600mg/day groups, respectively. Most discontinuations occurred during the titration phase. Like serious events, the most common cause of discontinuations were grouped under the SOC of nervous system disorders, with 2.5% withdrawing in the placebo group and 9.9% in the combined lacosamide groups for which there was also a dosage dependency. The most common nervous SOC, by preferred term, in descending order, were dizziness, ataxia, convulsion, and tremor. Except for convulsions, drug treated groups experienced greater rates then the placebo treated groups and there appeared to be a dose dependency. Dizziness and ataxia are rather common for this class of agents (i.e. sodium blocking anticonvulsants).

Discontinuations classified as CNS SOC in the epilepsy EP S1 pool was followed by GI disorders (3.2% drug Vs 0.8% placebo), general , Eye disorders (1.7% Vs 0.3% placebo), Psychiatric (1.6 % drug Vs 0%) and Ear and labyrinth disorders (1.4% drug Vs 1.0% placebo). Off interest no patients discontinued for reasons of cardiac disorders in placebo (0 of 364), but 0.4%(4 of 944 patients) did so in the lacosamide group. The numbers fro a cardiac signal may be too small, but this will be further discussed below. The most common contributing adverse event preferred term associated with GI was vomiting and nausea, contributing to over 90% of reporting. These symptoms are not uncommon for this class of agents (i.e. sodium blocking anticonvulsants). Visual preferred terms that contributed to the SOC were predominately diplopia and blurred vision, whereas vertigo and vestibular disorders contributed to all Ear and labyrinth disorders. Similar adverse events have been reported for other agents in this class of anticonvulsants. The overall rate of dropouts in EP S2 was similar to EP S1. Similar events led to drop out in the DNP database. Syncope led to dropout in both the EP and DNP populations and will be discussed below.

Common Adverse Events

A larger percent of patients experienced adverse events in the drug as compared to the placebo population in the EP S1 population (81% in drug Vs 65% in placebo). Common adverse events, greater in drug then placebo, were of similar nature as those reported that lead to

discontinuations: e.g. dizziness ataxia, nausea, vomiting, diplopia, vision blurred, etc. Fatigue somnolence, headache and memory impairment was also noted and occurred more frequently in drug then placebo. Adverse events generally followed a relatively obvious dose dependency. Events occurred in both, the titration and maintenance phase, but they were more frequent in the titration phase, particularly for those that were clearly dose related. Dr. Yasuda, safety team leader, noted that common adverse events in the DNP population were similar to the epilepsy population.

Laboratory Findings

Standard blood chemistries, hematology and urinalyses were collected throughout the studies. Dr Villabla notes that "evaluation of routine chemistry, hematology laboratory measurements and urinalyses did not reveal major issues of clinical concern in patients with partial-onset seizures..." She, however, notes that there was a slightly greater rate of ALT elevations 2X ULN in the control database for low dose, but this was not observed for higher doses or for AST. In EP S1 population ALT/AST >3X ULN occurred in 0.7% on LCM vs 0% on placebo, and was not associated with abnormal bilirubin. The elevations were reversible on withdrawal of LCM (although in 1 case the patient was lost to follow-up). Similar elevations of LFTs have been noted with other anticonvulsants. This CDTL believes that this can be labeled in the adverse event section (laboratories). No cases of liver failure were observed in either the epilepsy database or in the diabetic neuropathic pain population. Of note one patient was observed with markedly elevated LFTs associated with nephritis, which was interpreted as a multiorgan hypersensitivity and will be discussed below. One additional patient had a transient elevation of bilirubin associated with rash and mild eosinophilia. The bilirubin was elevated barely above the upper limit of normal and resolved within days of drug discontinuation. Becasue of the skin and eosinophila, Dr Villalba considered this as a potential multiorgan hypersensitivity response.

Vital signs

Dr Villabla notes that for study of tablets there was little or no effect on vital signs (SBP, DBP, heart rate, and weight), with therapeutic doses of LCM oral tablet in the epilepsy population. While orthostatic changes were not measured in phase 2/3 studies, they were measured in the TQTc study in healthy volunteers and there was no evidence of orthostatic hypotension in doses up to 800 mg/day.

Dr Villabla notes that in general the intravenous study design, presumably the lack of placebo control and small size, does not allow adequate safety comparisons with regard to vital signs. It is however noteworthy that 10% of patients receiving the 15-minute infusion and 2.5% of those receiving the 30-minute infusion presented at least one measurement of marked hypotension (SBP < 90 and drop ≥ 20mmHg or DBP <50 and drop ≥ 15 mmHg), perhaps suggesting an increased rate of hypotension with more rapid infusion. As noted above, there was a potential episode of arrhythmia, or vaso-vagal reaction with the more rapid infusion rates (15 minutes). b(4)

Adverse Events of Interest

Cardiac Adverse Events

As noted above, cardiac conduction abnormalities were identified in the non-clinical program. Becasue of this the Sponsor was asked to specifically discuss and analyze cardiac adverse events. Consistent with this the formal thorough QT (TQT) study revealed a dose-dependent increase in PR interval was observed. The maximum mean changes in PR interval on Day 6 (steady-state), observed at 1 hour post-dose, were 6.3ms, 13.6ms, and 18.2ms for the placebo, lacosamide 400 mg and lacosamide 800mg groups, respectively. There was no evidence in this study of an effect on the QRS interval. As noted above these changes were not associated with changes in blood pressure. The TQT study demonstrated a shortening of the QTc. At Tmax on day 6, the mean change in QTcI from baseline for LCM 400 mg/day compared to placebo was -9.4 msec with an upper one-sided 95% CI of -4.2; for 800 mg/day the values were -7.4 and -3.3 msec, respectively. This CDTL reviwer is under the impression that this is likely related to the ability of this drug to block sodium channels and indeed this CDTL reviwer has seen other TQT studies with similar channel activity produce similar QT prolongation. The significance of this shortening is not well understood, although it is known that patients with genetic short QT syndromes are at risk of ventricular fibrillation (without Torsades) and sudden death. Moreover, according to the IRT review of the TQT study, adequate data upon which to base a recommendation regarding labeling for products that shorten the QT interval do not currently exist. There was no obvious signal for this in the database to indicate sudden death or ventricular fibrillation (other then appear t to be explainable by SUDEP).

Dr. Villalba notes the percentage of patients with *any* potentially cardiac-related advere eevnt is 5.0% for lacosamide and 2.3% for placebo in EP S1. The difference was driven by a higher rate of rhythm and conduction disorders, mainly PR and QRS prolongation in the LCM group. There were 4 cases of first degree AV block in the LCM group (0.4%) vs 0% on placebo. Three subjects taking LCM presented conduction disorders that led to dropout (2 cases of bradycardia and 1 PR prolongation in a patient with sick sinus syndrome) in the EP S1 popultion. There were no cases of second degree AV block or serious arrhythmias in EP S1 or EP S2 popultions. In the DNP database, there was 1 case of second degree AV block in a patient with prolonged PR at baseline taking LCM 400 mg daily during the DNP open label studies, and an additional patient who had second degree AV block during telemetry monitoring after a syncopal episode during LCM titration with a dose of 600 mg. No QRS prolongation was observed in the DNP controlled database. In the placebo controlled studies in DNP there were 5 AEs of first degree AV block, 4 of atrial fibrillation, 3 of atrial flutter, and 1 nodal rhythm, all in the LCM treatment group. No such cases were observed in the placebo group.

The cases of PR prolongation and heart block are expected, based upon what is know about this drugs physiological effect. The reviwer of the Division of Cardio-Renal Products (DCRP) suggested that the increase in PR may result in clinically significant AV block and is particularly important in patients with pre-existing AV nodal disease and/or who are co-administered agents that block the AV node. DCRP recommends obtaining an ECG after LCM is titrated to steady state in such patients. They also suggested this effect may be potentiated in patients with myocardial injury (e.g. ischemia) because the associated increase in depolarization that may

enhance sodium channel blockade. DCRP believes that patients with diabetes and/or cardiovascular disease may be at increase risk of atrial fibrillation and/or atrial flutter following treatment with LCM. These will be addressed in labeling. Dr Yasuda suggests that a REMS might be considered. It is, however, noteworthy that a number of other medications (e.g. beta blockers, calcium channel blockers) can produce similar PR interval changes [redacted] This information should be included in the Warnings section of the label [redacted] b(5)

Syncope

Dr. Villalba noted that 11 cases of treatment emergent syncope/loss of consciousness were identified in the epilepsy population, three of them in the controlled phase (two on LCM and one on placebo). The differnce in the placebo trials does not allow the conclusion of a signal. Nonetheless, Dr Villabla noted that 27 cases of syncope were identified in the neuropathic pain population, 13 of them during the controlled studies (all in the LCM treatment group) and 14 in the open label studies. Most cases of syncope in the development program occurred at LCM doses of 600 mg/day. Four subjects presented syncope during the phase 1 studies [redacted] This suggested a signal for syncope, particularly in the neuropathic pain population. In one of the DNP cases, the patient had 2nd degree AV block identified with telemetry monitoring. This particular sensitivity to a potential cardiac event is consistent with DCRP's contention that injured cardiac tissue may be more prone to this drugs cardiac effect. Two cases had documented orthostatic hypotension on the same day of the event. Unfortunately most patients did not have ECGs performed or measurements of orthostatic blood pressure at the time of (or closely after) the syncope and consequently the mechanism is unclear. Based on the known effects of LCM in cardiac conduction, Dr. Villalba and Yasuda believe that an LCM-related cardiac cause for syncope cannot be ruled out. This CDTL agrees. In addition, Dr. Villalba suggests that if future clinical studies are performed, orthostatic changes in blood pressure should be measured, especially in patients who experience syncope or pre-syncope. In addition, both recommends that Holter monitoring should be considered in future clinical trial patients who experience syncope if the drug is not to be discontinued. These phenomena should be included in the Warnings [redacted] Drs Yasuda and Vilablla believes this may also be subject to a REMS. This issue was discussed at a varity of Divisional meetings and there was a consensus that , at this point a REMs need not be established [redacted] b(5) b(5)

Mood and Suicidality

Dr. Villalba also reported evidence of an effect of LCM on the mood of patients taking LCM as compared to placebo. Depression was the most frequent PT under the HLGT of Depressed mood disorders and disturbances (2.6% on LCM vs 0.5% on placebo), and there were other PT terms related to mood (depressed mood) and other mood disorders such as moodiness that also occurred more frequently in LCM than in placebo.

Dr. Villalba has identified a rate of suicidality-related events in the partial-onset seizure population as 0.5% (5/944) in patients taking LCM and 0.1% (1/781) in placebo patients. These rates are similar to what has been seen overall with AEDs as a class as reported in the January 2008 FDA alert (0.43% for AEDs in the epilepsy population Vs 0.22% on placebo).

Dr. Villalba notes that the Sponsor has not identified depression as an adverse event associated with LCM and recommends that depression should be prominent in the LCM labeling. Both Dr. Yasuda and this CDTL agrees. This information will be contained in suicidality information which is being requested for all anticonvulsant medications, which resulted from an extensive study of this issue in anticonvulsant controlled trials. Thus, Dr. Villalba recommends that lacosamide should carry the proposed class labeling Warnings and MedGuide for AEDs for the risk of suicidality. This CDTL agrees.

Multiorgan Hypersensitivity

As noted above there was a case that was suspected to represent possible multiorgan hypersensitivity. The case was associative with hepatitis and nephritis that occurred 12 days after final lacosamide exposure. LFTs achieved levels of 10 to 30 times the upper limits of normal and proteinurea was noted. No bilirubin was documented at the time of the event. Viral causes of hepatitis were ruled out. To better characterize this patient additional informtion was requested on this patient. The additional informtion indicted that bilirubin and eosinophiles were not elevated. Nonetheless, an immunologist who evaluated the subject concluded that this was a case of drug induced delayed hypersensitivity. Dr Villabla concludes that this represents a case of multiorgan hypersensitivity.

Informtion was also requested on a second case that may have represented multiorgan hypersensitivity. This case involved a death 2 months following the discontinuation of lacosamide following period of greater then one year of treatment. The patient suffered from "myocarditis (toxic damage to the myocardium) and alcoholic intoxication and toxic damage of the liver." However, investigator noted that the subject had no history of alcohol abuse. The date of onset of the toxic damage of the liver was unknown. Informtion received indicated that the actual date of the last dose of medication is unknown. This led Dr Villabla to conclude that, while the presentation of this syndrome after over one year of exposure is unusual, multiorgan hypersensitivity cannot be ruled out.

The Sponsor was also requested to search their clinical trial database to identify any other potential multiorgan hypersensitivity cases. Two cases were identified, which Dr. Vallbal believed may represent mild or aborted reactions. Many cases identified dis not provide adequate informtion to draw any conclusions. Both cases involved rash and eosinophilia and elevated LFTs which resolved on drug discontinuation.

Based upon this informtion, both Dr Villabla and Yasuda believe that this syndrome should be described in the Warnings section. This reviwer agrees.

b(5)

Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

b(4)

The CDTL recommends approval for Tablets (22253) and iv solution (22254).

Risk Benefit Assessment

There exists general agreement within the team that risk benefit ratio indicates that this drug should be approved.

Recommendation for Postmarketing Risk Management Activities

There is general agreement in the team that a MedGuide should be distributed for the issue of suicidal ideation, as it will be for other anticonvulsant drugs.

b(5)

There is some differnce in opinion regarding the issue of a MedGuide for Multiorgan hypersensitivity. Dr Villabla, in her review, notes that "MedGuide may help reduce the risk of serious multiorgan hypersensitivity reactions further." It should, however, be noted that this syndrome has been identified in with many anticonvulsants (indeed it was once referred to as anticonvulsant hypesentivity syndrome) and while it is included in the label of these agents no MedGuide had been adapted. Dr Villabla notes in her review that there is no way, at the present time, to determine if this syndrome is more or less common with this agent as compared to others. For these reasons this CDTL feels a MedGuide is not absolutely necessary. Meetings with Dr. Katz and Dr Temple indicate they concur. and labeling in the Warnings section is recommended.

b(5)

Pediatric(PREA)

The study of pediatric patients over 1 month will be deferred and that under 1 month will be waived.

Recommended Comments to Applicant

These are noted in the body of this review above. The reader should also examine the letter, which this reviwer concurs with.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The Sponsor intends to market the following formulations of this product for the adjunctive treatment of seizures associated with partial onset epilepsy:

- Tablets 50, 100 150, 200, 250 and 300 mg (22253)
- iv solution (22254)

b(4)

2.2 Currently Available Treatment for Indications

There are over 10 products labeled for this indication in patients >17 years of age (e.g. carbamazepine, oxcarbazepine, levetiracetam, zonisamide, gabapentin, lamictal, etc.).

2.3 Availability of Proposed Active Ingredient in the United States

This is an NME and the product is unavailable in the US.

2.4 Important Issues With Pharmacologically Related Products

The drug is a sodium channel blocker. These are widely used as anticonvulsants with known, principally CNS, toxicities. The therapeutic class of drugs are also known to produce a variety of idiosyncratic effects such as multiorgan hypersensitivity, blood dyscrasias, hepatotoxicity. But, the propensity to produce these effects varies with different agents within the class.

2.5 Presubmission Regulatory Activity

Lacosamide has been developed for two separate indications, partial onset seizures and pain associated with diabetic peripheral neuropathy (DPN). This reviewr from the Division of Neurology Prodcuts (DNP) will concentrate on efficacy results in partial onset seizures. That for DPN will be reviewed by Division of Anesthesia, Analgesia and Rheumatologic Products (DAARP). Safety data in this application has been reviewed by both division, and while this review will concentrate on safety in epilepsy, all data will be discussed. Because of specific interest in a potential cardiac signal the Division of Cardiovascular and Renal Products (DCRP) was asked to comment not only on the formal QT study but issues of PR prolongation and general cardiac safety.

2.6 Other Relevant Background Information

N/A

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

In CMC review of tablets (22253) submitted to DFS, performed by Drs. Shiromani and Sood, a recommendation of "approvable" was made pending responses to a letter containing questions (3/20/08) and the final Compliance and Environmental Assessment recommendations. No phase 4 commitments were made. A later memo (7/16/08) submitted to DFS recommended approval based upon acceptable responses to question and an acceptable Compliance report. The environmental Assessment found no concerns. Off note the Sponsor agreed to the following (although these do not appear to be phase 4 commitments):

b(4)

No issues CMC issues regarding the iv solution (22254) were identified. Inspections and microbiology were also found adequate. Approval was recommended by the CMC reviwer.

b(4)

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology review found no nonclinical issues and is recommending approval. They are, however recommending, the following phase 4 commitment:

> "Further assessment of lacosamide's effect on brain development is needed and that this assessment may be conducted postapproval. Such an assessment should certainly involve dosing in rat throughout the critical periods that correspond to the entire period of human fetal development with, perhaps, direct dosing of the neonate, and, as Dr. Fisher notes, the use of sensitive methods for assessing neurobehavioral function and expanded histopathological examination of the brain. "

- Early animal studies indicated potential cardiac effects involving slowing of atrio-ventricular and ventricular conductivity as evidence by the lacosamide-induced increase in PR interval and QRS duration. However, obvious hERG channel effects or QTc changes were not apparent. For this reason clinical cardiac adverse events were closely monitored. A formal QTc study was, off course also performed.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The following only refers to efficacy data. For safety data the reader is discussed by Dr Villalba's, safety reviewer, in her review.

4.1 Sources of Clinical Data

The Sponsor submitted 3 adequate and well controlled trials for review. Supportive studies were also included. The adequate well controlled trial consists of a phase 2b, dose finding study (SP667) and two phase 3 trials (SP754 and SP755). All three trials were of similar design (see below). The table below presents a summary of dose, time and numbers of patients studied in these protocols.

4.2 Tables of Clinical Studies

Trial number/Clinical development phase/Trial design	Number of subjects randomized to receive LCM[a]	Number of subjects randomized to receive placebo[a]	Maximum duration of treatment[b]
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97	21 weeks
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104	21 weeks
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163	18 weeks
Total	200mg/day: 270 400mg/day: 471 600mg/day: 203 Total: 944	364	

LCM=lacosamide

a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

b All 3 trials had a 12-week Maintenance Phase.

4.3 Review Strategy

This reviwer examined study reports. Data sets were and calculations were examined and confirmed by the statistics reviwer.

4.4 Data Quality and Integrity

Of the 3 pivotal efficacy trials, DSI inspected 2 sites in protocols SP754 and SP755. With one exception no problem was identified and sites were found to be completely acceptable. One site in Croatia inspected for protocol SP755 revealed a single protocol violation. Thus, one patient was maintained in the protocol at the studied dose, although he was initially tapered with an intent to withdraw the medication due too that adverse event. This CDTL does not believe this single event should adversely effect the conclusions of this study.

All 3 studies underwent changes in sample size during their implementation. One had a decrease in sample size because of unexpectedly fewer dropouts and 2 had an increase in sample size becasue a repeat calculation indicated that the original determination of standard deviation and effect size, based upon another anticonvulsant study, was incorrect. These changes were made without unblinding and, according to the statistics reviewer, Dr. Massie, are justified.

4.5 Compliance with Good Clinical Practices

No issues were identified.

4.6 Financial Disclosures

The Sponsor has provided financial interest information for clinical investigators participating in covered studies included in this Original New Drug Application, for lacosamide (SPM 927) indicated for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older and for the management of neuropathic pain associated with diabetic peripheral neuropathy. According to this, the $25,000 threshold for "payments of other sorts" was not exceeded in the case of any investigator. Moreover, no clinical investigator participating in the covered studies has a proprietary interest lacosamide. The Sponsor has also determined that no clinical investigator participating in the covered studies has a significant equity interest in Schwarz by using direct to investigator questionnaires.

5 CLINICAL PHARMACOLOGY

Dr. Fadiran and Zhang, clinical pharmacologists, performed the general clinical pharmacology review, while Dr Tandon reviewed the ——— iv solution formulations. b(4)

General PK Properties:

Lacosamide is a Biopharmaceutics Classification System (BCS) class 1 drug. Lacosamide tablets bioavailability was approximated to be about 100%. It is absorbed with a Tmax of 0.4 to 4 hours and a T1/2 of approximately 13 hours. This drug experiences <15% protein binding. The drug is

eliminated by the kidneys. Most of the drug in the urine is in the form of lacosamide (40%) or its metabolites with the major metabolite (SPM12809) making up 30% of that which is recovered. Its major metabolite is believed to be inactive. The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. But, the Sponsor determined that formation of the major metabolite, SPM 12809, is through the CYP2C19 pathway. The clinical pharmacology reviwer, however, notes that the relative role of P450 isoforms in the oxidative metabolism of lacosamide is not clear.

Drug-Drug Interactions:

In vitro studies indicate that lacosamide is not a significant inhibitor (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, 3A5), although it inhibits CYP2C19 to some extent. In vitro studies also indicated some induction of CYP 2C9 and 2C19, but only a small effect was noted in interaction studies with omeprazole (see below).

No interactions becasue of protein bindings was anticipated. Lacosamide was not a substrate for p-glycoprotein.

Definitive studies, in vivo, studies were performed on a number of potential concomitant drugs (anticonvulsants, oral birth control agents, hypoglycemic and cardio – active agents). The table below summarizes the conclusion, based upon CI of Cmax and AUC, drawn from these studies.

Effect of lacosamide on pharmacokinetics of other drugs:

Drug	Effect
Carbamazepine	None
Valproic acid	None
Digoxin	None
Oral Contraceptive	↑ Cmax of ethinylestradiol (~20%)
Omeprazole	None
Metformin	effect controversial, one group showed increase and the other group showed decrease in exposure of metformin. PD not studies. Clinical relevance not clear

Effect of other drugs on lacosamide pharmacokinetics:

Drug	Effect
Carbamazepine	None
Valproic acid	None
Omeprazole	No effect on LCM, but ↓ SPM12809 by 60%
Metformin	None

Population PK drug-drug interactions were also examined, which indicated that LCM exposure is reduced by 15-20% when lacosamide is co-administered with carbamazepine, phenobarbital, or phenytoin. The finding on carbamazepine contradicts the above noted findings and according the clinical pharmacology reviwer is difficult to interpret becasue of this disparity, lack of statistical significance of this effect and confounding covariates.

Special Populations:

The clinical pharmacology reviwer note that studies indicate that while no dose adjustments would be necessary for patients with mild to moderate renal impairment, patients with severe renal failure will require dose reductions. Studies indicate that similar adjustments would be necessary for patients with moderate hepatic impairment. Elderly patients experienced a 20-25% greater exposure when weight was taken into consideration. The clinical pharmacology reviewer felt that although this would not warrant dose adjustment on its own, becasue of increased incidence of impaired hepatic and renal function in this class of patients, some caution should be noted in this population. Although females experienced greater exposure, when weight was factored in this differnce disappeared. This led the clinical pharmacology reviwer to conclude that no adjustment is necessary. There were no racial differences in exposure when adjusted for body weight. Poor CYPC19 metabolizers were examined in a small study. No substantial differnce was noted in the plasma concentrations of the parent drug with extensive metabolizers. However, there was a significant differences (75 to 85%) observed in the SPM 12809 metabolite. Because of this metabolites low level, in comparison to the parent, this was not thought to be significant enough for a dose adjustment

b(4)

and iv Solution formulations

As all efficacy studies were performed using a tablet formulation it was necessary to establish equivalent bioavailability between this formulation and iv solution

b(4)

The sponsor conducted two bioequivalent studies in healthy subjects evaluating the bioequivalence of solution for infusion at different infusion rates versus the oral tablets (Study SP645 and SP658). Dr Tandon, the clinical pharmacology reviewer notes that such studies demonstrated:

- 15 minute IV infusion of 200 mg versus tablets (2x100 mg):
  BE with respect to AUC(0-t)
  Not BE with respect to Cmax
- 30 minute IV infusion of 200 mg versus tablets (2x100 mg):

BE with respect to both AUC(0-t) and Cmax

- 60 minute IV infusion of 200 mg versus tablets (2x100 mg):
  BE with respect to both AUC(0-t) and Cmax

In addition to the above definitive bioequivalence studies the sponsor performed two studies in epilepsy patients already on a presumed therapeutic dose of lacosamide tablets. The intravenous formulation was substituted for tablets for a period of up to 5 days. The intravenous formulation infused over various times (10, 15 and 30 minutes). Minimal differences in the Ctrough and Cmax values for the 10, 15 and 30 minute infusion were observed. Dr Tandon concluded that it could be concluded, "the 10, 15, 30 and 60 minute infusions at a given dose give comparable plasma concentrations of LCM."

OCP Recommendations:

- OCP found the application acceptable "provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert."
- A phase IV commitment is recommended to "determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19. "

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor wishes to obtain labeling for adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older.

6.1.1 Methods

The Sponsor has submitted what they refer to as "3 adequate and well controlled trials" for review. Additional studies from supportive studies are included. The adequate well controlled trial consists of a phase 2b, dose finding study (SP667) and two phase 3 trials (SP754 and SP755). All three trials were of similar design (see below). The table below presents a summary of dose, time and numbers of patients studied in these protocols.

Trial number/Clinical development phase/Trial design	Number of subjects randomized to receive LCM[a]	Number of subjects randomized to receive placebo[a]	Maximum duration of treatment[b]
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97	21 weeks
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104	21 weeks
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163	18 weeks
Total	200mg/day: 270 400mg/day: 471 600mg/day: 203 Total: 944	364	

LCM=lacosamide

a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

b All 3 trials had a 12-week Maintenance Phase.

The Sponsor notes 4 additional trials as supportive for the claim of efficacy. All trials were uncontrolled and open-label studies. Study SP607 compared seizures during baseline with that following treatment for a maximum period and consists of 14 days in 91 patients. Studies SP615, SP756 and SP774 were simple open label extension trials of the 3 pivotal trials. A total of 1,048 patients were examined in these studies.

6.1.2 General Discussion of Endpoints

Primary Endpoint

The primary endpoint adopted for US and European studies where different and based upon the standards typically used for those institutions. The dual primary endpoints were agreed upon by the FDA in an end of phase 2 meeting. The FDA assigned endpoint was the change in partial seizure frequency per 28 days from baseline to the maintenance period.

Seizure frequency was calculated by the formula:

SF = (Number of Seizures) x (28 / D)

Where SF= seizure frequency, D is the number of days. The manner that baseline seizure frequency was calculated was different between the initial dose ranging study, SP667 and the two phase 3 studies, SP754 and SP755. These differences were protocol driven. Thus for SP667 baseline values were based upon the complete 8 week baseline period, but for SP754 and SP755 baseline value was based upon the last 56 days of the baseline period.

For patients who discontinued during maintenance phase an LOCF frequency value was calculated. If the patient dropped out prior to entering the maintenance period an LOCF value for the titration period was calculated.

Seizure clusters were dealt with in a special fashion. Thus, if a seizure cluster occurred the cluster was reported and the highest recorded daily number of seizures of that seizure type (i.e. cluster) during that phase for that subject during that phase. If no other cluster occurred during that phase the value used was that reported for the single cluster.

Statistical analysis of the seizure frequency change was performed on the log-transformed seizure frequency[2] based on an ANCOVA model with terms for treatment and pooled site. Log-transformed average seizure frequency during the Baseline Phase was used as the covariate. The seizure frequency between treatment and placebo was compared using LS means. Percentage reduction over placebo was calculated by: 100 x (1 - exp[LSM Treatment – LSM Placebo]), where LSM is the least squares mean from the analysis. This analysis was previously described in the Sponsor's statistical analysis plans. The log transformation allows a normalization of data. An alternative plan was to perform an analysis on ranked seizure frequencies, if normalization was not achieved.

Criteria for statistical significance were $P \leq 0.05$.

The primary analysis used the full analysis set (FAS) which was defined as all subjects who returned at least 1 post-baseline diary. A per protocol set (PPS) was also analyzed. This was a subset of patients in the FAS without major protocol violation as defined during a blinded review,

2 ,Log transformation was based upon the formula ln(x+1), where x is equal to the seizure frequency.

The primary outcome described above and its method of analysis is similar to those used for the approval of a number of drugs. The single differnce is the fact that only the maintenance period as opposed to the full treatment (titration period + maintenance period) was used. It is doubtful that this may influence statistical significance. Moreover an analysis of the full treatment period is performed as a secondary endpoint.

The EMEA primary outcome was analyzed as a secondary outcome by the FDA (see below).

Secondary Endpoints

- 50 percent responder rate was calculated as the percent of subjects experiencing a ≥50% reduction in partial onset seizure frequency from Baseline to the Maintenance Phase. This was also used by the EMEA as a primary endpoint.
- The change in partial seizure frequency per 28 days from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases).
- Proportion of subjects experiencing a ≥50% reduction in partial seizure frequency from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases). Other responder rates were also examined (≥75%, and ≥25%).
- Percent change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase and from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases).
- Proportion of subjects experiencing a ≥25% to <50%, 50% to <75%, or ≥75% reduction in partial seizure frequency per 28 days from Baseline to the Maintenance Phase and from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases).
- Proportion of subjects experiencing no change in partial seizure frequency per 28 days (ie, between <25% reduction and <25% increase in partial seizure frequency) and the proportion of subjects experiencing ≥25% increase in partial seizure frequency from Baseline to the Maintenance Phase and from Baseline to the Treatment Phase (ie, Titration + Maintenance Phases).
- Proportion of seizure-free days during the Maintenance Phase for subjects who entered the Maintenance Phase.
- Proportion of subjects who achieved "seizure-free status" (yes/no) during the Maintenance Phase for subjects who completed the Maintenance Phase.
- Response to treatment by seizure type.
- Clinical Global Impression of Change.
- Quality of Life in Epilepsy-31.

6.1.3 Study Design

As noted above all three studies were of a similar design. They were all multi-institutional, double-blind, and placebo-control, parallel cohort, adjunctive treatment studies in adults. Trials were rather similar in design. The schedule of evaluations was similar across studies.

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ON ORIGINAL

Procedures	Baseline Phase (8 weeks)			Treatment Phase (18 weeks)												
				Titration Phase (6 weeks)						Maintenance Phase (12 weeks)						
Visit [1]	V1	V2	V3	T1	V4	T2	V5	T3	V6[4]	T4	V7	T5	V8	T6	V9[7]/ EW[8]	Unscheduled Visit[9]
Weeks in Trial	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16	18	
Informed Consent	X															
In-/Exclusion Criteria	X															
Medical History	X															
Concomitant AEDs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (complete)	X		X												X	
Physical Exam (brief)							X		X							X
Vital Signs (including BP and HR)	X	X	X		X		X		X		X		X		X	X
Body Weight	X	X	X		X		X		X		X		X		X	X
Neurological Exam (complete)	X		X												X	
Neurological Exam (brief)							X		X							X
ECG (12-lead) [2]	X		X		X		X		X		X		X		X	
Laboratory Tests:																
Clinical Chemistry/Hematology	X		X		X		X		X		X		X		X	X
Urinalysis	X		X						X		X				X	X

Procedures	Baseline Phase (8 weeks)			Treatment Phase (18 weeks)												
				Titration Phase (6 weeks)						Maintenance Phase (12 weeks)						
Visit [1]	V1	V2	V3	T1	V4	T2	V5	T3	V6[4]	T4	V7	T5	V8	T6	V9[7]/ EW[8]	Unscheduled Visit[9]
Weeks in Trial	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16	18	
Pregnancy Test	X[5]		X[U,6]				X[U]		X[U]		X[U]		X[U]		X[5]	
Concomitant AED Plasma concentrations [3]	X		X						X		X				X	X
SPM 927 Plasma concentration [3]			X		X		X		X		X				X	X
Clinical Global Impression Change															X	
Patient's Global Impression Change															X	
Seizure Severity Scale			X												X	
QOLIE-31			X												X	
Call IVRS	X		X		X		X		X		X		X		X	
Randomization			X													
Dispense Trial Medication			X[5]		X		X		X		X		X		X	
Trial Medication Return					X		X		X		X		X		X	X[10]
Dispense Subject Diary	X	X	X		X		X		X		X		X		X	
Subject Diary Return		X	X		X		X		X		X		X		X	X[10]
AE Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of epilepsy surgery/VNS	X														X	

BP, blood pressure; EW, early withdrawal; HR, heart rate; IVRS, interactive voice response system; S, serum; T, telephone contact; U, urine; V, Visit; VNS, vagal nerve stimulation.

[1] For all visits a time window of ±2 days relative to Baseline Visit 3 is applicable.

[2] 12-lead ECGs will be recorded at the times provided below.

Visit 1: one assessment at any time.

Visit 3: three assessments 15 minutes apart prior to dosing of trial medication.

Visits 4 to 9: one assessment at any time after dosing of trial medication.

[3] Blood samples for analysis of concomitant AED plasma concentrations and/or SPM 927 will be drawn at the appropriate times:

Visit 1: samples for plasma concentrations of concomitant AEDs will be collected along with hematology samples.

Visit 3: samples for plasma concentrations of concomitant AEDs and SPM 927 will be collected along with hematology samples prior to dosing of trial medication.

Visits 4 to 9: samples for plasma concentrations of concomitant AEDs and SPM 927 will be collected along with hematology samples at any time after dosing of trial medication.

[4] At Visit 3 a urine dipstick pregnancy test should be performed. The result of the urine dipstick test must be negative prior to administration of the first dose of trial medication.

[5] At Visit 3, subjects should take the first dose of trial medication in the clinic.

[6] If subject is back-titrated at Week 6, then subject will enter the Maintenance Phase with the reduced dose of trial medication.

[7] At the end of Visit 9, all subjects who complete the Maintenance Phase will be offered the opportunity to enroll in an open-label extension trial of SPM 927. Subjects who choose to enroll in the open-label extension trial will proceed to a 2-week Transition Phase to a dose of 200mg/day SPM 927. Subjects who choose not to enter the open-label extension trial or who do not complete the Maintenance Phase will proceed to a 3-week Taper Phase.

[8] Subjects who discontinue from the trial after randomization at Visit 3 but before completing Visit 9 should complete the Visit 9 assessments at the Early Withdrawal Visit.

[9] If an unscheduled clinic visit is needed (eg, due to an AE), then the assessments noted must be performed. An ECG may be performed at the investigator's discretion.

[10] The subject should bring the diary and trial medication to the clinic for review.

A sample of the Sponsor's schedule for trial SP754 is presented in the two tables and footnotes below. Initial screening was performed on the first day of the baseline period. Seizure diaries were provided at this time and patients were instructed in their use. Patients then entered an 8 week baseline phase. They were randomized following this period if they continued to fulfill inclusion/exclusion criteria (there was a requirement for a minimal seizure frequency during this period). Patients entered the treatment phase following randomization which consisted of a titration and a maintenance period. The titration periods in SP 667 and SP754 were of 6 weeks duration and that of SP 755 were of 4 weeks in duration. All titrations proceeded at the rate of 100 mg qD (in a BID divided dose) every week. Final dosage and numbers of patients are presented in the table below. All doses were administered as an evenly divided BID dosage form. Subjects who could not tolerate their final dose were permitted one back titration by 100 mg during the titration period. The titration period was followed by a 12 week maintenance period in all studies. No back titration was permitted during this period. After the study was completed patients were given a choice to continue on lacosamide in an open label study at a dose of 200 mg/day. If they so decided, they would undergo a blind transition period where they were titrated to a dose of 200 mg/day. If they declined they would undergo a down-titration that would proceed at a rate of 200 mg/day every week.

Trial number/clinical development phase/trial design	Number of subjects randomized to receive LCM[a]	Number of subjects randomized to receive placebo[a]
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163

Inclusion/Exclusion Criteria

Inclusion/exclusion was identical for SP 754 and SP755. Those for SP667 were similar to the latter. These are presented below. These were similar in all studies with minor exceptions. The SP 754 and SP755inclusion/exclusion criteria are presented below, exceptions for SP667 are indicated in brackets.

Inclusion Criteria:

- Subject was informed and given ample time and opportunity to think about his/her participation and had given his/her written informed consent.
- Subject was willing and able to comply with all trial requirements
- Subject was male or female between 16 and 70 years of age (inclusive). [Subjects in SP667 were required to be 18 to 65 years of age, inclusive.]
- Subject had a diagnosis of epilepsy with simple partial seizures and/or complex-partial seizures with or without secondary generalization according to the International

Classification of Epileptic Seizures (1981). The results of at least 1 prior EEG and 1 MRI or CT scan should have been consistent with diagnosis of partial seizures due to epilepsy.

- Subject was observed to have partial onset seizures for at least the last 2 years despite prior therapy with at least 2 AEDs (concurrently or sequentially) and was observed to have on average at least 4 partial onset seizures per 28 days with seizure-free phases no longer than 21 days in the 8-week period prior to entry into the Baseline Phase. In the case of simple partial seizures, only those with motor signs were counted towards meeting the inclusion criteria.
- Subject was on a stable dosage regimen of at least 1, but no more than 3 AEDs, with or without additional concurrent stable VNS. [Subjects in SP667 were to be on 1 to 2 AEDs.] The VNS must have been in place for at least 6 months prior to trial entry. The dosage of concomitant AED therapy and the settings of VNS must have been kept constant for a period of at least 4 weeks prior to entry into the Baseline Phase.

Exclusion Criteria

- Subject had received LCM in a previous trial.
- Subject was currently participating or had participated within the last 2 months in any trial of an investigational drug or experimental device.
- Subject had a history of chronic alcohol or drug abuse within the previous 2 years.
- Subject had any medical or psychiatric condition, which in the opinion of the investigator, could have jeopardized the subjects' health or would have compromised the subject's ability to participate in this trial.
- Subject had a known hypersensitivity to any component of the investigational product(s) as stated in the protocol. [This was not an exclusionary criterion for SP667.]
- Pregnant or nursing women and/or those of childbearing potential who were not surgically sterile, 2 years postmenopausal or did not practice 2 combined methods of contraception, unless sexually abstinent, during the duration of the trial.
- Subject had alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin levels greater than or equal to 2 times the upper limit of normal (ULN).
- Subject had impaired renal function, i.e., creatinine clearance (CL_{cr}) was lower than 50mL/min, at Visit 1. [For SP667, a serum creatinine level $\geq$2 times the upper limit of normal was the exclusionary criteria.]
- Subject with a diastolic blood pressure (BP) less than 50mmHg or greater than 105mmHg or pulse less than 50 beats per minute (bpm) or greater than 110bpm, after 3 minutes in a sitting position. Subject with heart rate by ECG less than 50bpm or greater than 110bpm.
- Subject had confirmed clinically significant abnormality in ECG, including prolonged QTc (Bazett's, machine-read) interval defined as $\geq$450ms for males and $\geq$470ms for females.
- Subject had a known history of severe anaphylactic reaction or serious blood dyscrasias.
- Subject with nonepileptic events, including psychogenic seizures that could have been confused with seizures.

- Subject with seizures that were uncountable due to clustering (i.e., an episode lasting less than 30 minutes in which several seizures occur with such frequency that the initiation and completion of each individual seizure could not be distinguished) during the 8-week period prior to trial entry.
- Subject with a history of primary generalized seizures.
- Subject with a history of status epilepticus within the 12-month period prior to entry.
- Subject with concomitant treatment of felbamate or previous felbamate therapy within the last 6 months prior to trial entry.
- Subject had taken vigabatrin in the preceding 6 months. (Note: A subject with a history of vigabatrin treatment must have had a visual perimetry test at least 6 months following conclusion of the treatment that shown either no damage or a visual field defect associated with 1 of the following 2 conditions: 1) there was no change from a visual field test done at some point while the subject was taking vigabatrin, or 2) there was no change from a visual field test done shortly after stopping vigabatrin administration.) [The stipulation of the 6 month period was not included SP667.]
- Subject with a progressive structural lesion in the central nervous system (CNS) or a progressive encephalopathy.
- Subject had any other clinically significant disease, surgical condition or recent chronic consumption of non-AED medications (within the preceding 4 weeks prior to trial entry), that might reasonably be expected to interfere with drug absorption, distribution, metabolism or excretion.
- Subject was taking 1 of the following medications influencing the CNS on a regular basis within 4 weeks prior to trial entry: neuroleptics, monoamine oxidase (MAO) inhibitors, barbiturates (**except** for medication taken as concomitant anticonvulsant treatment), and narcotic analgesics.

6.1.4 Efficacy Findings

Study SP667

Patient Disposition

A table listing the disposition of randomized patients in all dose groups is presented below. Not shown here is the fact that 45 patients failed randomization during screening. A large percent (42%) of patients in the highest dose group (600 mg/day) failed to complete the study. Most of these patients dropped out during the titration phase. Seventy one percent of those discontinuing in this dose did so for reasons of adverse events. Discontinuations in the 200 and 400 mg/day dose groups where less (21 and 26%), but still twice that of what was observed in the placebo group (11%). Like the high dose group, the majority of these were a result of adverse event.

Withdrawal for reasons of adverse events followed an obvious dose response. It is also noteworthy that 15 to 22 percent of patients in the drug groups required a step back in dose during the titration period. This was also observed in placebo but at one-third to one half the rate. Except for "withdrew of consent" other reasons for study discontinuation were lower and evenly matched between placebo and the dosage groups. "Withdrew of consent" may have been more common in the two higher doses and were slightly nor common.

Summary of Subject Disposition
Population: Safety Set

	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
	n (%)	n (%)	n (%)	n (%)
Randomized	97 (100)	107 (100)	108 (100)	106 (100)
Completed Titration	92 (95)	95 (89)	89 (82)	71 (67)
Reduced dose prior to entering Maintenance	7 (7)	16 (15)	16 (15)	23 (22)
Completed Maintenance	88 (91)	88 (82)	83 (77)	62 (58)
Completed trial	86 (89)	85 (79)	80 (74)	61 (58)
Discontinued trial prematurely	11 (11)	22 (21)	28 (26)	45 (42)
Reasons for discontinuation[a]:				
Protocol deviations	2 (2)	1 (<1)	1 (<1)	3 (3)
Lack of efficacy	1 (1)	1 (<1)	1 (<1)	2 (2)
Adverse event	5 (5)	16[c] (15)	20 (19)	32 (30)
Poor compliance[b]	0 (0)	2 (2)	2 (2)	3 (3)
Withdrew consent	3 (3)	3 (3)	7 (6)	5 (5)
Lost to follow-up	1 (1)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (<1)	1 (<1)

[a]More than one primary reason for discontinuation may have been recorded by the investigator.
[b]Note that unsatisfactory compliance could refer to poor treatment compliance or poor compliance with trial procedures.
[c]Note that based on the definition of the dates for phases, 4 subjects (Subjects, 15017, 15019, 17724, 18802) had all AEs leading to discontinuation start during a phase which occurred after the Treatment Phase, ie during Taper or Transition. Therefore, these 4 subjects are not counted among the subjects discontinued during the Treatment Phase due to AEs in Table 114.
Data Source: Table 3

Patient Demographics

Major demographic features of randomized patients are presented in the table below. Except for a slight preponderance for females in drug treatment groups, demographic characteristics are reasonably well balanced between placebo and drug treatment groups. Most patients were designated as "Caucasian."

Parameter	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
Age (years)				
Mean (SD)	38.9 (11.11)	39.9 (11.71)	41.2 (11.61)	39.4 (10.53)
Min, Max	19, 66	18, 65	18, 68	18, 64
Weight (kg)				
Mean (SD)	79.5 (20.90)	74.5 (17.16)	77.5 (18.63)	75.7 (19.40)
Min, Max	45.0, 155.4	45.0, 129.3	43.0, 142.0	42.2, 143.8
Gender				
Male n (%)	47 (48)	46 (43)	53 (49)	45 (42)
Female n (%)	50 (52)	61 (57)	55 (51)	61 (58)
Ethnic origin				
Caucasian n (%)	88 (91)	98 (92)	100 (93)	101 (95)
Black n (%)	6 (6)	4 (4)	5 (5)	2 (2)
Asian n (%)	0 (0)	2 (2)	0 (0)	0 (0)
Other n (%)	3 (3)	3 (3)	3 (3)	3 (3)

The table below presents both presumed causes of seizures in randomized patients and the categorization of such seizures. All such features where generally well balanced across placebo and dosage treatment groups.

APPEARS THIS WAY ON ORIGINAL

Population: Safety Set

Parameter	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
Mean time since diagnosis (years)	24.6	25.1	24.7	23.6
Etiology				
Genetic Propensity n (%)	11 (11)	6 (6)	7 (6)	7 (7)
Congenital Abnormality n (%)	5 (5)	4 (4)	9 (8)	15 (14)
Ante- and Perinatal Injury n (%)	10 (10)	6 (6)	9 (8)	10 (9)
Trauma n (%)	15 (15)	14 (13)	26 (24)	17 (16)
Infections n (%)	12 (12)	8 (7)	8 (7)	10 (9)
Vascular Causes n (%)	2 (2)	8 (7)	4 (4)	4 (4)
Toxic Causes n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Degenerative Causes n (%)	1 (1)	4 (4)	2 (2)	1 (<1)
Idiopathic Causes n (%)	33 (34)	36 (34)	31 (29)	31 (29)
Other n (%)	17 (18)	23 (21)	22 (20)	22 (21)
Number of subjects with simple partial seizures n (%)	33 (34)	48 (45)	41 (38)	50 (47)
Number of subjects with complex partial seizures n (%)	83 (86)	101 (94)	94 (87)	96 (91)
Number of subjects with partial seizures with secondary generalization n (%)	73 (75)	79 (74)	77 (71)	70 (66)

Patient Baseline Features

The table below presents concomitant antiepileptic medications for the randomized patients. The most common medications included carbamazepine, levetiracetam and lamotrigine. Drugs were well balanced across the placebo and all dosage treatment groups.

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ON ORIGINAL

Concomitant AED	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
	n (%)	n (%)	n (%)	n (%)
Carbamazepine	34 (35)	29 (27)	23 (21)	43 (41)
Levetiracetam	25 (26)	41 (38)	31 (29)	30 (28)
Lamotrigine	28 (29)	25 (23)	35 (32)	27[a] (25)
Topiramate	16 (16)	19 (18)	28[a] (26)	19 (18)
Oxcarbazepine	16 (16)	23 (21)	16 (15)	16 (15)
Phenytoin sodium	7 (7)	7 (7)	14 (13)	10 (9)
Valproate sodium	6 (6)	14[a] (13)	11 (10)	7 (7)
Phenytoin	6[a] (6)	10 (9)	8 (7)	8 (8)
Valproic acid	7 (7)	7 (7)	4 (4)	10[a] (9)
Gabapentin	5 (5)	5 (5)	6 (6)	7 (7)
Phenobarbital	3 (3)	2 (2)	8 (7)	6 (6)
Zonisamide	8 (8)	6 (6)	6 (6)	2 (2)
Lorazepam	4 (4)	5 (5)	3 (3)	6 (6)
Valproate semisodium	3 (3)	4 (4)	2 (2)	7 (7)

APPEARS THIS WAY
ON ORIGINAL

Parameter	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
Age (years)				
Mean (SD)	38.9 (11.11)	39.9 (11.71)	41.2 (11.61)	39.4 (10.53)
Min, Max	19, 66	18, 65	18, 68	18, 64
Weight (kg)				
Mean (SD)	79.5 (20.90)	74.5 (17.16)	77.5 (18.63)	75.7 (19.40)
Min, Max	45.0, 155.4	45.0, 129.3	43.0, 142.0	42.2, 143.8
Gender				
Male n (%)	47 (48)	46 (43)	53 (49)	45 (42)
Female n (%)	50 (52)	61 (57)	55 (51)	61 (58)
Ethnic origin				
Caucasian n (%)	88 (91)	98 (92)	100 (93)	101 (95)
Black n (%)	6 (6)	4 (4)	5 (5)	2 (2)
Asian n (%)	0 (0)	2 (2)	0 (0)	0 (0)
Other n (%)	3 (3)	3 (3)	3 (3)	3 (3)

Primary Endpoint

The table below presents the median seizure frequency during baseline and maintenance period as well as the median change from baseline for the FAS. These data demonstrates an apparent effect of lacosamide.

Median seizure frequency	Placebo N=96	SPM 927 200mg/day N=107	SPM 927 400mg/day N=107	SPM 927 600mg/day N=105
Baseline	11	13	13	11
Maintenance Endpoint	10	10	7	8
Change from Baseline[a]	-1	-3	-3	-4

The following table presents the calculated percentage reduction over placebo and statistical analysis as described above (see primary endpoint). These data indicates statistical significance

in only the 400 and 600 mg dosages, with little obvious dose response relation in these same dosages.

Comparison of SPM 927 to Placebo	% Reduction Over Placebo	P-value	95% CI for % Reduction Over Placebo
600mg/day	21.3%	0.0084**	(6.0, 34.1)
400mg/day	28.4%	0.0023**	(11.3, 42.2)
200mg/day	14.6%	0.1010	(-3.2, 29.4)

A similar analysis on the PPS reveals a potential effect at 200 mg/day as well. This is presented in the table below. The effects are of larger magnitude. Interestingly, the shape of the dose response is an inverted "U." This may be suggestive of a dose response curve at 200 to 400 mg/day. The reason for the reduction in effect from 400 to 600 mg/day may have resulted from the large number of patients in the 600 mg group who dropped out during the titration period.

Comparison of SPM 927 to Placebo	% Reduction Over Placebo	P-value	95% CI for % Reduction Over Placebo
600mg/day	31.6%	0.0002**	(16.9, 43.6)
400mg/day	39.3%	<0.0001**	(24.7, 51.1)
200mg/day	21.5%	0.0112*	(5.4, 34.8)

Secondary endpoint

- *50% responder rate:* Results of the 50% responder rate for the FAS is presented in the table below. Results were similar to that observed for the primary endpoint.

Treatment	50% Responder	Unadjusted difference compared with placebo	Odds ratio	P-value for odds ratio
Placebo	21%	NA	NA	NA
600mg/day	49%	28.0%	3.9	0.0004**
400mg/day	49%	28.2%	3.7	0.0002**
200mg/day	38%	16.9%	2.3	0.0214*

- *Reduction in seizure frequency form baseline to treatment phase (tiitration and maintenance):* These data also revealed results similar to that of the primary endpoint (see below table).

Comparison of SPM 927 to Placebo	% Reduction Over Placebo	P-value	95% CI for % Reduction Over Placebo
600mg/day	21.3%	0.0033**	(7.8, 32.8)
400mg/day	20.3%	0.0100*	(5.3, 32.9)
200mg/day	10.8%	0.1650	(-4.9, 24.2)

- *Other responder rates:* The FAS analysis is presented for this data below. These data are consistent with that of the primary endpoint. The results are consistent with a therapeutic effect. Comparing treatment groups to placebo, the drug groups did not appear to produce an increase in seizure frequency and the reductions in seizures were at the expense, as compared to placebo, to no change or increase in frequency.

% Reduction	Placebo N=96	SPM 927 200mg/day N=107	SPM 927 400mg/day N=107	SPM 927 600mg/day N=105
	n (%)	n (%)	n (%)	n (%)
At least 75%	6 (6)	12 (11)	24 (22)	17 (16)
At least 50%	21 (22)	35 (33)	44 (41)	40 (38)
At least 25%	36 (38)	56 (52)	61 (57)	68 (65)
No change	41 (43)	35 (33)	23 (21)	16 (15)
Increase in frequency[2]	19 (20)	16 (15)	23 (21)	21 (20)

- *Proportion of subjects who achieved seizure-free status during the maintenance phase:* These data, for the FAS, is presented in the table below. While few patients achieved seizure free status, only those on drug where observed to be seizure free.

	Placebo N=96	SPM 927 200mg/day N=107	SPM 927 400mg/day N=107	SPM 927 600mg/day N=105
	n (%)	n (%)	n (%)	n (%)
Number of subjects who completed the Maintenance Phase	88 (92)	88 (82)	83 (78)	62 (59)
Number of Subjects who were seizure-free during the Maintenance Phase	0 (0)	1 (1)	5 (6)	1 (2)

- *Change in the percentage of seizure free days:* The table below presents the change in the percent of seizure free days. As apparent this was increased by drug. Statistical analysis of this using an ANCOVA model with terms for treatment and region and a covariate of the baseline value was performed and was found statistically significant for the two higher doses.

Median percentage of seizure-free days	Placebo N=91	SPM 927 200mg/day N=95	SPM 927 400mg/day N=89	SPM 927 600mg/day N=70
Baseline (%)	71	63	70	66
Maintenance Endpoint (%)	77	74	85	80
Change from Baseline[a] (%)	3	6	12	12

- *Clinical Global Impression of Change (CGIC):* Results of the CGIC for the FAS are presented in the table below. While there was a trend for improvement in the 400 and 600 mg/day group, this effect did not prove to be statistically significant (Chi-square).

Number (%) of subjects who had:	Placebo N=96	SPM 927 200mg/day N=107	SPM 927 400mg/day N=107	SPM 927 600mg/day N=105
	n=91	n=94	n=89	n=68
Improved	55 (60%)	57 (61%)	63 (71%)	50 (74%)
No change	35 (38%)	34 (36%)	22 (25%)	10 (15%)
Worsened	1 (1%)	3 (3%)	4 (4%)	8 (12%)
p-value	NA	0.8103	0.3872	0.7996

- *Change in Seizure Frequency by Seizure Type (from baseline to maintenance):* These data for the FAS are presented in the table below. A consistent trend for a therapeutic drug effect was seen on all subclasses of partial seizure disorders.

Subjects with seizure type during Baseline	Percent change from Baseline seizure frequency at maintenance endpoint[a]			
	Placebo N=96	SPM 927 200mg/day N=107	SPM 927 400mg/day N=107	SPM 927 600mg/day N=105
Simple partial	-17% (n=25)	-23% (n=34)	-41% (n=32)	-27% (n=44)
Complex partial	-15% (n=79)	-32% (n=95)	-41% (n=88)	-42% (n=90)
Partial seizures with secondary generalization	-20% (n=47)	-34% (n=45)	-60% (n=45)	-69% (n=38)
Complex partial and partial seizures with secondary generalization	-11% (n=92)	-30% (n=103)	-43% (n=104)	-43% (n=96)

- *Quality of Life in Epilepsy-31:* The quality of life changes (data not shown) as measured by this tool were small and inconsistent. No conclusions can be made from this measure.

Study SP764

Patient Disposition

Patient disposition in this study is presented in the table below. Rates of discontinuation are twice as much for the 400 mg/day dose as for placebo as was in the prior described study. The 600 mg/day dose however experienced somewhat lower rates of discontinuation in this trial as compared to the previous: compare 33% in the present study to 42% in the prior study, but gereter then that observed for the lower dose in this study. As in the prior study, the majority of discontinuations were a result of adverse events. Other reasons for discontinuing were well distributed between groups. Like the prior study, the majority of patients who withdrew from the study did so during the titration phase.

	Placebo N=104	LCM 400mg/day N=204	LCM 600mg/day N=97	Total N=405
	n (%)	n (%)	n (%)	n (%)
Randomized	104	204	97	405
Completed Titration	98 (94.2)	168 (82.4)	72 (74.2)	338 (83.5)
Completed Maintenance	95 (91.3)	162 (79.4)	65 (67.0)	322 (79.5)
Completed trial	90 (86.5)	161 (78.9)	65 (67.0)	316 (78.0)
Completed Transition	87 (83.7)	153 (75.0)	65 (67.0)	305 (75.3)
Completed Taper	3 (2.9)	8 (3.9)	0	11 (2.7)
Discontinued trial prematurely	14 (13.5)	43 (21.1)	32 (33.0)	89 (22.0)
Reasons for discontinuation[a]:				
Adverse event	5 (4.8)	36 (17.6)	26 (26.8)	67 (16.5)
Lack of efficacy	1 (1.0)	2 (1.0)	0	3 (0.7)
Withdrew consent	4 (3.8)	2 (1.0)	4 (4.1)	10 (2.5)
Protocol deviation	2 (1.9)	1 (0.5)	2 (2.1)	5 (1.2)
Unsatisfactory compliance	1 (1.0)	2 (1.0)	0	3 (0.7)
Lost to follow-up	1 (1.0)	0	0	1 (0.2)
Other	0	0	0	0

LCM=lacosamide

a Subjects could have more than 1 reason for discontinuation.

Note: Subject 14308 (LCM 600mg/day) completed the Transition Phase but did not complete the Maintenance Phase; this subject is counted as an early dicontinuation from the Maintenance Phase and is not included in the Transition Phase summary.

Patient Demographics

Demographics for all participating patients (safety set) are presented in the table below. Demographic features were generally well balanced across treatment groups, although there was a very slight disproportional representation elderly (≥65 years) in the drug treatment groups in general and specifically in the 400 mg/day group, which was probably insignificant. Few total patients, however, were older then 65 years of age. Unlike the prior study more patients were characterized as "black" (8- 10%).

Parameter	Placebo N=104	LCM 400mg/day N=204	LCM 600mg/day N=97	Total N=405
Age (years)				
Mean (SD)	38.1 (11.96)	39.1 (12.37)	36.8 (11.76)	38.3 (12.13)
Min, Max	16.0-61.0	17.0-71.0	16.0-69.0	16.0-71.0
Age (years) n (%)				
<65	104 (100.0)	197 (96.6)	96 (99.0)	397 (98.0)
≥65	0	7 (3.4)	1 (1.0)	8 (2.0)
Gender n (%)				
Male	49 (47.1)	104 (51.1)	47 (48.5)	200 (49.4)
Female	55 (52.9)	200 (49.0)	50 (51.5)	205 (50.6)
Weight (kg)				
Mean (SD)	75.4 (18.48)	83.9 (21.65)	80.8 (21.26)	81.0 (21.03)
Min, Max	43.1-163.3	38.6-187.8	39.9-143.3	38.6-187.8
BMI (kg/m^2)				
Mean (SD)	26.4 (5.50)	29.3 (7.52)	28.2 (7.13)	28.3 (7.05)
Race n (%)				
White	84 (80.8)	166 (81.4)	80 (82.5)	330 (81.5)
Black	12 (11.5)	18 (8.8)	8 (8.2)	38 (9.4)
Asian	1 (1.0)	3 (1.5)	1 (1.0)	5 (1.2)
Other	7 (6.7)	17 (8.3)	8 (8.2)	32 (7.9)

BMI=body mass index; LCM=lacosamide; Max=maximum; Min=minimum; SD=standard deviation

Patient Baseline Features

The table below presents seizure classification and etiology for the safety set. These are generally similarly distributed between treatment groups and similar to those observed in study SP667.

Parameter	Placebo N=104	LCM 400mg/day N=204	LCM 600mg/day N=97	Total N=405
Mean time since diagnosis (years)	25.4	24.5	23.4	24.5
Etiology n (%)				
Genetic propensity	10 (9.6)	16 (7.8)	8 (8.2)	34 (8.4)
Congenital abnormality	8 (7.7)	16 (7.8)	11 (11.3)	35 (8.6)
Ante- and perinatal injury	7 (6.7)	9 (4.4)	7 (7.2)	23 (5.7)
Trauma	23 (22.1)	35 (17.2)	14 (14.4)	72 (17.8)
Infection	16 (15.4)	20 (9.8)	15 (15.5)	51 (12.6)
Vascular causes n (%)	6 (5.8)	11 (5.4)	1 (1.0)	18 (4.4)
Toxic causes	0	1 (0.5)	0	1 (0.2)
Degenerative causes n	1 (1.0)	1 (0.5)	0	2 (0.5)
Idiopathic causes	41 (39.4)	88 (43.1)	39 (40.2)	168 (41.5)
Other	9 (8.7)	24 (11.8)	11 (11.3)	44 (10.9)
Number of subjects with simple partial seizures n (%)	49 (47.1)	97 (47.5)	43 (44.3)	189 (46.7)
Numbers of subjects with complex partial seizures n (%)	93 (89.4)	181 (88.7)	80 (82.5)	354 (87.4)
Number of subjects with partial seizures with secondary generalization n (%)	78 (75.0)	146 (71.6)	74 (76.3)	298 (73.6)

LCM=lacosamide

The table below presents concomitant anticonvulsant medications used in the safety set. Generally drug use was similar across groups except for a mild preponderance in the use of levetireactam and topiramate in the placebo group.

Concomitant AED	Placebo N=104	LCM 400mg/day N=204	LCM 600mg/day N=97	Total N=405
	n (%)	n (%)	n (%)	n (%)
Levetiracetam	48 (46.2)	80 (39.2)	32 (33.0)	160 (39.5)
Lamotrigine	38 (36.5)	72 (35.3)	36 (37.1)	146 (36.0)
Carbamazepine	22 (21.2)	54 (26.5)	26 (26.8)	102 (25.2)
Oxcarbazepine	27 (26.0)	36 (17.6)	23 (23.7)	86 (21.2)
Phenytoin meds[b]	18 (17.3)	42 (20.6)	16 (16.5)	76 (18.8)
Topiramate	24 (23.1)	36 (17.6)	13 (13.4)	73 (18.0)
Valproate meds[a]	20 (19.2)	31 (15.2)	17 (17.5)	68 (16.8)
Zonisamide	13 (12.5)	32 (15.7)	14 (14.4)	59 (14.6)
Phenobarbital meds[c]	4 (3.8)	17 (8.3)	6 (6.2)	27 (6.7)
Gabapentin	4 (3.8)	12 (5.9)	7 (7.2)	23 (5.7)
Lorazepam	3 (2.9)	9 (4.4)	5 (5.2)	17 (4.2)
Clonazepam	1 (1.0)	8 (3.9)	5 (5.2)	14 (3.5)

AED=antiepileptic drug; LCM=lacosamide

a Valproate includes valproate semisodium and valproic acid.

b Phenytoin includes phenytoin, fosphenytoin sodium, and phenytoin sodium.

c Phenobarbital includes primidone, phenobarbital and phenobarbital sodium.

Note: Subjects taking more than 1 form of valproate, phenytoin, or phenobarbital are only counted once per medication.

Number of concomitant medications (1, 2 or 3) was generally similarly distributed across treatment groups (data not shown). Most patients were taking 2 anticonvulsants (55%).

Primary Endpoint

The table below presents the median seizure frequency during baseline and maintenance period as well as median change from baseline for the FAS. Baseline seizure frequency was somewhat lower for the 400 mg/day group as compared to the other two experimental groups. A numerically greater reduction is apparent when drug was compared to placebo. There is a potential numerical trend in dose response relation, but the effect is smaller the prior study (SP667).

Median seizure frequency	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
Baseline	15.0	11.5	16.5
Maintenance Phase	11.8	6.9	9.7
Change from Baseline[a]	-2.9	-3.9	-5.3

LCM=Lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

Note: One subject (subject 11008 in the LCM 400mg/day group) reported aberrantly high number of seizures (daily seizure counts ranging from 423 to 963 during the first 2 weeks of the Titration Phase). This subject was discontinued during the Titration Phase due to the unsatisfactory compliance. Accurate counting of individual seizures by this subject was considered unrealistic by the Sponsor. Upon query the investigator confirmed the subject was able to count each individual seizure.

The table below presents the calculated percentage reduction over placebo and statistical analysis of difference, which corrected for baseline differences (see primary endpoint). Both dosages resulted in a statistically significant improvement over placebo with 600 mg/day producing only a marginally greater effect then 400 mg/day. The magnitude of effect was similar to the observed effect in SP667 for like dosages.

LCM Treatment Group	% reduction over placebo	p-value	95% CI for % reduction over placebo
400mg/day	21.6	0.0078**	(6.3, 34.5)
600mg/day	24.6	0.0061**	(7.8, 38.3)

**significant at the 0.0100 level

CI=confidence interval; LCM=lacosamide

An analysis of patients in the per protocol set resulted in a similar effect for the 400 mg/day dose but a more obvious increase defect in the 600 mg/day dose. These data for these are presented below.

LCM Treatment Group	% reduction over placebo	p-value	95% CI for % reduction over placebo
400mg/day	20.6	0.0152*	(4.4, 34.0)
600mg/day	33.0	0.0023**	(13.6, 48.1)

*significant at the 0.0500 level; **significant at the 0.0100 level

Secondary Endpoints

- *50% responder rate:* Results for the 50% responder rate for the FAS populations presented in the table below. Results were similar to that observed for frequency changes, with both doses producing a significant differnce as compared to placebo and 600 mg/day only marginally superior in magnitude then 400 mg/day. The magnitude of effect is similar to that observed in Study SP667.

Treatment	50% responder rate (%)	Unadjusted difference compared with placebo	Odds ratio	p-value for odds ratio
Placebo	18.3	NA	NA	NA
LCM 400mg/day	38.3	20.0	2.8	0.0004**
LCM 600mg/day	41.2	23.0	3.2	0.0005**

**significant at the 0.0100 level

LCM=lacosamide; NA=not applicable

- *Reduction in seizure frequency from baseline to treatment phase (titration and maintenance):* The FAS analysis that compares the reduction in frequency for placebo versus the full treatment phase is presented below. Results are similar to the primary endpoint, but smaller in magnitude as may be excepted as it include an analysis period (titration) in which doses where on average lower.

LCM Treatment Group	% reduction over placebo	p-value	95% CI for % reduction over placebo
400mg/day	19.0	0.0043**	(6.4, 29.9)
600mg/day	19.9	0.0086**	(5.5, 32.1)

**significant at the 0.0100 level

CI=confidence interval; LCM=lacosamide

- *Other responder rates:* The FAS analysis is presented below. Responder rates >50% were greater in both dosage groups as compared to the placebo. Neither dose produces an increase in seizures rate over that seen with placebo. These data are consistent with the primary endpoint and consistent with a therapeutic effect.

Response level	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
	n (%)	n (%)	n (%)
≥75%	8 (7.7)	41 (20.4)	21 (21.6)
≥50%-<75%	11 (10.6)	36 (17.9)	19 (19.6)
≥25%-<50%	30 (28.8)	44 (21.9)	21 (21.6)
No change[a]	38 (36.5)	54 (26.9)	22 (22.7)
Increase in frequency[b]	17 (16.3)	26 (12.9)	14 (14.4)

LCM=lacosamide

a No change reflects a reduction in seizure frequency per 28 days of less than 25% or an increase in seizure frequency per 28 days less than 25%.

b Increase in frequency reflects an increase in seizure frequency per 28 days greater than or equal to 25%.

- *Proportion of subjects who achieved seizure-free status during the maintenance phase:* This analysis for the FAS population is presented below. While small numbers became seizure free, the increase in numbers over placebo is consistent with a therapeutic effect. The effects observed here are similar to stud SP667.

	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
	n (%)	n (%)	n (%)
Number of subjects who completed the Maintenance Phase	95 (91.3)	160 (79.6)	62 (63.9)
Number of subjects who were seizure-free during the Maintenance Phase	0	4 (2.5)	5 (8.1)

LCM=lacosamide

Note: Percentages for number of subjects who were seizure-free during the Maintenance Phase is calculated from the number of subjects who completed the Maintenance Phase.

- *Change in the percentage of seizure free days:* The table below presents the change in the percent seizure free days for the FAS population. Both doses produced an increase in the median percent of seizure free days. The higher dose appeared to have a marginally greater effect then the lower dose. Both dosages proved to be statistically significant from placebo (ANCOVA with terms for treatment and region and covariate of baseline value). The effect was of similar magnitude as those observed in study SP667.

Median percentage of seizure-free days	Placebo N=98	LCM 400mg/day N=168	LCM 600mg/day N=72
Baseline (%)	64.3	71.4	65.8
Maintenance Phase (%)	74.7	82.7	80.4
Change from Baseline[a] (%)	5.7	9.1	12.8

LCM=lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

Note: Only subjects with Maintenance Phase data are included in this analysis.

- *Clinical Global Impression of Change (CGIC) during maintenance:* Analysis of the CGIC for the FAS population is presented below. There was a trend for greater improvement in patients receiving drugs. Both dose groups produced a similar effect. Unlike the trend observed in study SP667 this effect was found to be statistically significant (Mantel-Haenszel and Chi-square).

Number (%) of subjects who had:	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
	n=98	n=168	n=71
Improved[a]	52 (53.1)	127 (75.6)	58 (81.7)
No change	41 (41.8)	32 (19.0)	9 (12.7)
Worsened[a]	4 (4.1)	9 (5.4)	4 (5.6)
p-value[b]	NA	0.0007	0.0005
p-value[c]	NA	0.0128	0.0029

LCM=lacosamide; NA=not applicable

a The category of improved represents the sum of very much improved, much improved, and minimally improved. The category of worsened represents the sum of minimally worse, much worse, and very much worse.

b Pairwise testing for categories of improved, no change, and worsened was based on a mean score Mantel-Haenszel Chi-square test using standardized midranks.

c Treatment comparisons for the proportions of much improved (much and very much improved) subjects is based on Chi-square test.

Note: n refers to the number of subjects evaluated in this analysis, and is the denominator for the percentages.

Note: CGIC is assessed at the last Maintenance Phase visit or at the Early Termination Visit for subjects who prematurely discontinue from the trial.

- Patent's Global Impression of Change (PGIC) during maintenance: Similar results were observed for the PGIC as were observed for CGGIC in the FAS population. Changes were statistically significant for both doses (Mantel-Haenszel and Chi-square). These are presented in the table below.

Number (%) of subjects who had:	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
	n=98	n=168	n=71
Improved[a]	49 (50.0)	117 (69.6)	56 (78.9)
No change	38 (38.8)	27 (16.1)	6 (8.5)
Worsened[a]	9 (9.2)	15 (8.9)	5 (7.0)
p-value[b]	NA	0.0012	<0.0001
p-value[c]	NA	<0.0001	<0.0001

LCM=lacosamide; NA=not applicable

a The category of improved represents the sum of very much improved, much improved, and minimally improved. The category of worsened represents the sum of minimally worse, much worse, and very much worse.

b Pairwise testing for categories of improved, no change, and worsened was based on a mean score Mantel-Haenszel Chi-square test using standardized midranks.

c Treatment comparisons for the proportions of much improved (much and very much improved) subjects is based on Chi-square test.

Note: n refers to the number of subjects evaluated in this analysis, and is the denominator for percentages.

Note: PGIC is assessed at the last Maintenance Phase visit or at the Early Termination Visit for subjects who prematurely discontinue from the trial.

- *Change in seizure frequency by seizure type:* The median percent change in frequency from baseline to maintenance for various partial seizure subtypes is presented in the table below. No trend was apparent for simple partial but a therapeutic trend was apparent for complex partial and secondary generalized. As may be recalled, this differs from study SP776, where a trend was observed for all seizure types.

Subjects with seizure type during Baseline	Percent reduction from Baseline seizure frequency at Maintenance Phase[a]		
	Placebo N=104	LCM 400mg/day N=201	LCM 600mg/day N=97
Simple partial	47.6% (n=41)	34.9% (n=73)	22.6% (n=35)
Complex partial	22.2% (n=86)	38.7% (n=170)	44.4% (n=75)
Partial (simple or complex) seizures with secondary generalization	14.3% (n=45)	59.4% (n=84)	93.0% (n=47)
Complex partial or partial (simple or complex) seizures with secondary generalization[b]	21.5% (n=95)	39.4% (n=195)	47.4% (n=91)

LCM=lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

b Subjects with complex partial seizures or partial (simple or complex) seizures with secondary generalization are only counted once in this by seizure type analysis.

- *Quality of Life in Epilepsy-31:* Changes in the overall scale was in the wrong direction (toward worsening) but were of very small magnitude and was not consistent across subscales (data not shown).

Study SP765

Patient Disposition

Patient disposition in this study is presented in the table below. Rates of discontinuation are twice as much for the 400 mg/day dose as for placebo as was observed in prior described studies. The rates for discontinuation in the 200 mg group were only slightly greater in the 200 mg/day group. This was different for the other study that examined the 200 mg (SP667) dose which exhibited similar rates to the 400 mg/day dose. As in the prior study, the majority of discontinuations in the 400 mg/day group were a result of adverse events. Other reasons for discontinuing were well distributed between groups. Most discontinuance in the 400 mg/day group occurred during the titration period.

	Placebo N=163	LCM 200mg/day N=163	LCM 400mg/day N=159	Total N=485
	n (%)	n (%)	n (%)	n (%)
Randomized	163 (100)	163 (100)	159 (100)	485 (100)
Completed Titration	148 (90.8)	151 (92.6)	136 (85.5)	435 (89.7)
Completed Maintenance	143 (87.7)	137 (84.0)	123 (77.4)	403 (83.1)
Completed Transition	135 (82.8)	130 (79.8)	116 (73.0)	381 (78.6)
Completed Taper	6 (3.7)	6 (3.7)	6 (3.8)	18 (3.7)
Completed trial	141 (86.5)	136 (83.4)	122 (76.7)	399 (82.3)
Discontinued trial prematurely	22 (13.5)	27 (16.6)	37 (23.3)	86 (17.7)
Reasons for discontinuation[a]:				
Adverse event	9 (5.5)	10 (6.1)	25 (15.7)	44 (9.1)
Lack of efficacy	3 (1.8)	2 (1.2)	0	5 (1.0)
Withdrew consent	5 (3.1)	8 (4.9)	5 (3.1)	18 (3.7)
Protocol deviation	1 (0.6)	2 (1.2)	2 (1.3)	5 (1.0)
Unsatisfactory compliance	2 (1.2)	2 (1.2)	3 (1.9)	7 (1.4)
Lost to follow-up	3 (1.8)	1 (0.6)	0	4 (0.8)
Other	2 (1.2)	2 (1.2)	2 (1.3)	6 (1.2)

LCM=lacosamide

a Subjects could have more than 1 reason for discontinuation.

Patient Demographics

Demographics for all participating patients (safety set) are presented in the table below. Except for somewhat more females in the 400 mg/dose group demographic features were generally well balanced across treatment groups. Few patients were characterized as "non-white." Few patients were older then 65 years and all of these were in the drug treatment groups. The prior study (SP754) had the highest percentage of "non-white" with 8-10% patients characterized as "black."

Parameter	Placebo N=163	LCM 200mg/day N=163	LCM 400mg/day N=159	Total N=485
Age (years)				
Mean (SD)	38.5 (10.93)	36.9 (11.70)	37.9 (12.96)	37.8 (11.88)
Min, Max	17, 63	16, 66	16, 70	16, 70
Age (years) n (%)				
<65	163 (100)	161 (98.8)	155 (97.5)	479 (98.8)
≥65	0	2 (1.2)	4 (2.5)	6 (1.2)
Gender n (%)				
Male	91 (55.8)	90 (55.2)	69 (43.4)	250 (51.5)
Female	72 (44.2)	73 (44.8)	90 (56.6)	235 (48.5)
Weight (kg)				
Mean (SD)	74.7 (17.06)	74.9 (16.93)	72.2 (16.90)	74.0 (16.97)
Min, Max	40.0, 122.3	39.5, 137.0	36.0, 116.0	36.0, 137.0
BMI (kg/m^2)				
Mean (SD)	25.9 (5.01)	25.2 (4.79)	25.3 (5.09)	25.4 (4.96)
Race n (%)				
White	162 (99.4)	162 (99.4)	157 (98.7)	481 (99.2)
Black	0	1 (0.6)	0	1 (0.2)
Asian	1 (0.6)	0	2 (1.3)	3 (0.6)
Other	0	0	0	0

BMI=body mass index; LCM=lacosamide; Max=maximum; Min=minimum; SD=standard deviation

Patient Baseline Features

The table below presents seizure classification and etiology for the safety set. These are generally similarly distributed between treatment groups and similar to those observed in the prior two studies.

Parameter	Placebo N=163	LCM 200mg/day N=163	LCM 400mg/day N=159	Total N=485
Mean time since diagnosis (years)	21.1	22.9	22.8	22.3
Etiology n (%)				
Genetic propensity	0	4 (2.5)	1 (0.6)	5 (1.0)
Congenital abnormality	16 (9.8)	18 (11.0)	21 (13.2)	55 (11.3)
Ante- and perinatal injury	17 (10.4)	22 (13.5)	18 (11.3)	57 (11.8)
Trauma	23 (14.1)	20 (12.3)	22 (13.8)	65 (13.4)
Infections	15 (9.2)	14 (8.6)	23 (14.5)	52 (10.7)
Vascular causes	5 (3.1)	8 (4.9)	6 (3.8)	19 (3.9)
Toxic causes	1 (0.6)	0	0	1 (0.2)
Degenerative causes	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Idiopathic causes	47 (28.8)	42 (25.8)	35 (22.0)	124 (25.6)
Other	43 (26.4)	38 (23.3)	38 (23.9)	119 (24.5)
Number of subjects with simple partial seizures n (%)	61 (37.4)	67 (41.1)	58 (36.5)	186 (38.4)
Numbers of subjects with complex partial seizures n (%)	138 (84.7)	142 (87.1)	146 (91.8)	426 (87.8)
Number of subjects with partial seizures with secondary generalization n (%)	130 (79.8)	125 (76.7)	127 (79.9)	382 (78.8)

LCM=lacosamide

The table below presents concomitant anticonvulsant medications used in the safety set. Generally drug use was similar across groups.

Concomitant AED	Placebo N=163	LCM 200mg/day N=163	LCM 400mg/day N=159	Total N=485
	n (%)	n (%)	n (%)	n (%)
Carbamazepine	73 (44.8)	86 (52.8)	73 (45.9)	232 (47.8)
Valproate[a]	58 (35.6)	50 (30.7)	51 (32.1)	159 (32.8)
Lamotrigine	51 (31.3)	45 (27.6)	52 (32.7)	148 (30.5)
Topiramate	44 (27.0)	50 (30.7)	43 (27.0)	137 (28.2)
Levetiracetam	30 (18.4)	29 (17.8)	37 (23.3)	96 (19.8)
Oxcarbazepine	26 (16.0)	26 (16.0)	23 (14.5)	75 (15.5)
Clonazepam	19 (11.7)	19 (11.7)	15 (9.4)	53 (10.9)
Phenytoin[b]	14 (8.6)	13 (8.0)	12 (7.5)	39 (8.0)
Gabapentin	10 (6.1)	14 (8.6)	9 (5.7)	33 (6.8)
Clobazam	9 (5.5)	15 (9.2)	12 (7.5)	36 (7.4)

AED=antiepileptic drug; LCM=lacosamide

a Valproate includes valproate sodium, valproic acid, valpromide, and ergenyl chrono.

b Phenytoin includes phenytoin and phenytoin sodium.

Approximately 50% of patients were on two concomitant medications and approximately 37% were on three medications.

Primary Endpoint

The table below presents the median seizure frequency during baseline and maintenance period as well as median change from baseline for the FAS. Baseline seizure frequency was somewhat lower in the placebo group as compared to the other two experimental groups. A numerically greater reduction is apparent in the two drug treatment groups as compared to the placebo group. The effect of the 400 mg group is similar to study SP764 but smaller then SP667.

Median seizure frequency per 28 days by treatment
Population: Full Analysis Set

Median seizure frequency	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
Baseline	9.9	11.5	10.3
Maintenance Phase	7.6	7.2	6.7
Change from Baseline[a]	-2.6	-3.6	-3.4

LCM=lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

Note: One subject (Subjet 108302 in the LCM 200mg/day treatment group) reported an unusually high number of seizures (approximately 300 seizures per day on average) during the 8-week Baseline Phase and 14 days of the Titration Phase. This subject discontinued during the Titration Phase (while still taking placebo) at SCHWARZ BIOSCIENCES' request due to the high number of seizures reported by this subject. Upon query the investigator confirmed the subject was able to count each individual seizure.

Data source: Table 8.1.1

For the subjects in the FAS, the median Baseline seizure frequency per 28 days for placebo, LCM 200mg/day, and LCM 400mg/day was 9.9, 11.5, and 10.3, respectively. The median seizure frequency per 28 days for the Maintenance Phase for these treatment groups was 7.6, 7.2, and 6.7, respectively.

The table below presents the calculated percentage reduction over placebo and statistical analysis of difference, which corrected for baseline differences (see primary endpoint). Both dosages produced nominally similar effects that resulted in a statistically significant improvement over placebo. The magnitude of effect fro the 400 mg/day dose was about one third to one half less then that observed in study SP764 and SP667, respectively, but the 200 mg/day dose produce an effect similar in magnitude to that observed in SP667 for the 200 mg/day dose.

LCM treatment group	% reduction over placebo	p-value	95% CI for % reduction over placebo
200mg/day	14.4	0.0223*	(2.2, 25.1)
400mg/day	15.0	0.0325*	(1.4, 26.8)

*significant at the 0.0500 level

An analysis, similar to that performed in the latter table, of patients in the per protocol set resulted in statistically significant effects for both doses, but with a potential dose response relation. These data are presented in the table below.

LCM treatment group	% reduction over placebo	p-value	95% CI for % reduction over placebo
200mg/day	13.6	0.0430*	(0.5, 24.9)
400mg/day	19.2	0.0119*	(4.6, 31.6)

*significant at the 0.0500 level

CI=confidence interval; LCM=lacosamide

Secondary Endpoints

- *50% responder rate:* Results for the 50% responder rate for the FAS populations presented in the table below. Results were similar to that observed for frequency changes, with both doses producing a significant difference as compared to placebo. The 400 mg/day group was marginally greater then the 200 mg/day dose group. The magnitude of effect is similar to that observed in Study SP667 in the 200 mg/day dose group but smaller then the 400 mg/day dose group in that study. The magnitude of effect of the latter dose was similar to that for study SP764.

Treatment	50% responder rate (%)	Unadjusted difference compared with placebo	Odds ratio	p-value for odds ratio
Placebo	25.8	NA	NA	NA
LCM 200mg/day	35.0	9.2	1.6	0.0735
LCM 400mg/day	40.5	14.7	2.0	0.0063**

**significant at the 0.0100 level

LCM=lacosamide; NA=not applicable

- *Reduction in seizure frequency from baseline to treatment phase (titration and maintenance):* The FAS analysis that compares the reduction in frequency for placebo versus the full treatment phase is presented below. Results are similar to the primary endpoint, but with a potentially more apparent dose response relation.

LCM treatment group	% reduction over placebo	p-value	95% CI for % reduction over placebo
200mg/day	12.3	0.0294*	(1.3, 22.1)
400mg/day	15.1	0.0164*	(3.0, 25.7)

*significant at the 0.0500 level

CI=confidence interval; LCM=lacosamide

- *Other responder rates:* The FAS analysis is presented below. Responder rates >50% were greater in both dosage groups as compared to the placebo. Neither dose produces an increase in seizures rate over that seen with placebo. These data are consistent with the primary endpoint and consistent with a therapeutic effect.

Response level	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
	n (%)	n (%)	n (%)
≥75%	19 (11.9)	24 (15.0)	24 (15.2)
≥50%-<75%	22 (13.8)	32 (20.0)	40 (25.3)
≥25%-<50%	36 (22.6)	42 (26.3)	36 (22.8)
No change[a]	52 (32.7)	39 (24.4)	33 (20.9)
Increase in frequency[b]	30 (18.9)	23 (14.4)	25 (15.8)

LCM=lacosamide

a No change reflects a reduction in seizure frequency per 28 days of less than 25% or an increase in seizure frequency per 28 days less than 25%.

b Increase in frequency reflects an increase in seizure frequency per 28 days greater than or equal to 25%.

- *Proportion of subjects who achieved seizure-free status during the maintenance phase:* This analysis for the FAS population is presented below. While small numbers of apteints became seizure free, the increase in numbers over placebo is consistent with a therapeutic effect.

	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
	n (%)	n (%)	n (%)
Number of subjects who completed the Maintenance Phase	143 (89.9)	137 (85.6)	123 (77.8)
Number of subjects who were seizure-free during the Maintenance Phase	3 (2.1)	5 (3.6)	3 (2.4)

LCM=lacosamide

- *Change in the percentage of seizure free days:* The table below presents the change in the percent seizure free days for the FAS population. Both doses produced a marginal

increase in the median percent of seizure free days over placebo. The higher dose appeared to have a marginally greater effect then the lower dose. Only the 400 mg/day dose group proved to be statistically significant from placebo (ANCOVA with terms for treatment and region and covariate of baseline value). The lower dose was nearly statistically significant (p=0.055).

Median percentage of seizure-free days	**Placebo N=148**	**LCM 200mg/day N=149**	**LCM 400mg/day N=136**
Baseline (%)	71.4	69.6	72.7
Maintenance Phase (%)	80.1	81.0	82.1
Change from Baseline[a] (%)	7.1	8.2	9.3

LCM=lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

- *Clinical Global Impression of Change (CGIC) during maintenance:* Analysis of the CGIC for the FAS population is presented below. There was a trend for greater improvement in patients receiving 400 mg/day. The effect of the lower dose was not obvious. Neither dose was observed to be statistically significant unlike study SP764, but similar to study SP667.

Number (%) of subjects who had:	**Placebo N=159**	**LCM 200mg/day N=160**	**LCM 400mg/day N=158**
	n=148	**n=151**	**n=136**
Improved[a]	82 (55.4)	88 (58.3)	90 (66.2)
No change	54 (36.5)	52 (34.4)	38 (27.9)
Worsened[a]	11 (7.4)	11 (7.3)	8 (5.9)
p-value[b]	NA	0.6834	0.0813
p-value[c]	NA	0.3495	0.3313

LCM=lacosamide; NA=not applicable

a The category of improved represents the sum of very much improved, much improved, and minimally improved. The category of worsened represents the sum of minimally worse, much worse, and very much worse.

b Pairwise testing for categories of improved, no change, and worsened was based on a mean score Mantel-Haenszel Chi-square test using standardized midranks.

c Treatment comparisons for the proportions of much improved (much and very much improved) subjects was based on Chi-square test.

- Patent's Global Impression of Change (PGIC) during maintenance: Similar results were observed for the PGIC as were observed for CGGIC in the FAS population. These are presented in the table below.

Number (%) of subjects who had:	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
	n=148	n=151	n=136
Improved[a]	85 (57.4)	87 (57.6)	89 (65.4)
No change	42 (28.4)	37 (24.5)	29 (21.3)
Worsened[a]	17 (11.5)	22 (14.6)	14 (10.3)
p-value[b]	NA	0.8876	0.1851
p-value[c]	NA	0.5177	0.1183

LCM=lacosamide; NA=not applicable

a The category of improved represents the sum of very much improved, much improved, and minimally improved. The category of worsened represents the sum of minimally worse, much worse, and very much worse.

b Pairwise testing for categories of improved, no change, and worsened was based on a mean score Mantel-Haenszel Chi-square test using standardized midranks.

c Treatment comparisons for the proportions of much improved (much and very much improved) subjects was based on Chi-square test.

- *Change in seizure frequency by seizure type:* The median percent change in frequency from baseline to maintenance for various partial seizure subtypes is presented in the table below. No obvious trend, and perhaps even an increase in frequency, was apparent for simple partial, but numbers of patients with this type of seizures were small. There was a potential therapeutic effect in the high dose group for complex partial seizures. The most obvious therapeutic trend for both doses was secondarily generalized seizures.

Subjects with seizure type during Baseline	Percent reduction from Baseline seizure frequency at Treatment Phase[a]		
	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
Simple partial	32.2% (n=44)	27.5% (n=52)	10.3% (n=36)
Complex partial	21.1% (n=130)	30.0% (n=134)	37.5% (n=140)
Partial (simple or complex) seizures with secondary generalization	21.8% (n=72)	45.8% (n=61)	36.7% (n=56)
Complex partial or partial (simple or complex) seizures with secondary generalization[b]	17.3% (n=148)	29.6% (n=146)	37.0% (n=154)

LCM=lacosamide

a Change from Baseline represents median of individual subject changes from Baseline.

b Subjects with complex partial seizures or partial (simple or complex) seizures with secondary generalization are only counted once in this by seizure type analysis.

- *Quality of Life in Epilepsy-31:* Changes in the overall scale tended toward improvement, but these effects were very small (data not shown).

6.1.5 Clinical Microbiology

No issues were identified (see CMC).

6.1.6 Efficacy Conclusions

The results of the primary endpoint (percent change from baseline to maintenance) over placebo is presented for all three trials in the table below. The percent reduction from placebo is based upon logarithmically transformed data, but is actually very close to arithmetic percent changes. From these data it is apparent that both the 400 and 600 mg daily dose resulted in a significant reduction in seizures from placebo. This was also the conclusion of the Pharmaco-metrics reviewer, by Dr. Zhu, who noted that in a nonlinear regression least squares modeling response curve started to flatten out beyond the median exposure of 400 mg dose. From the data below, and as per Dr Zhu's analysis, there is no obvious additional therapeutic benefit observed for the 600 mg/day as compared to 400 mg/day. In the 2 studies that examined the 200 mg/day dose a therapeutic trend was noted. This effect, however, was statistically significant for only one

study. This reviewer believes that the 200 mg dose is therapeutic in some patients but may on average have a smaller effect resulting in an inconsistent statistical finding between both studies.

Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	14.6%	0.1010	(-3.2, 29.4)
LCM 400mg/day (N=107)	28.4%	0.0023**	(11.3, 42.2)
LCM 600mg/day (N=105)	21.3%	0.0084**	(6.0, 34.1)
SP754			
LCM 400mg/day (N=201)	21.6%	0.0078**	(6.3, 34.5)
LCM 600mg/day (N=97)	24.6%	0.0061**	(7.8, 38.3)
SP755			
LCM 200mg/day (N=160)	14.4%	0.0223*	(2.2, 25.1)
LCM 400mg/day (N=158)	15.0%	0.0325*	(1.4, 26.8)

As noted above, the change in frequency from baseline to maintenance phase is not a typical endpoint. The more conventional endpoint of change from baseline to the experimental period (titration + maintenance) was examined as a secondary endpoint. Data from this analysis is presented below, and differs little from the primary endpoint. This serves as an excellent sensitivity analysis to the Sponsor's endpoint.

Trial/Comparison of LCM to placebo	% reduction over placebo	P-value	95% CI for % reduction over placebo
SP667			
LCM 200mg/day (N=107)	10.8%	0.1650	(-4.9, 24.2)
LCM 400mg/day (N=107)	20.3%	0.0100*	(5.3, 32.9)
LCM 600mg/day (N=105)	21.3%	0.0033**	(7.8, 32.8)
SP754			
LCM 400mg/day (N=201)	19.0%	0.0043**	(6.4, 29.9)
LCM 600mg/day (N=97)	19.9%	0.0086**	(5.5, 32.1)
SP755			
LCM 200mg/day (N=160)	12.3%	0.0294*	(1.3, 22.1)
LCM 400mg/day (N=158)	15.1%	0.0164*	(3.0, 25.7)

The statistical significance of secondary endpoint, 50% responder rate (the EMEA primary analysis), exhibited results identical, in terms of which doses were statically significant from placebo, to the primary endpoints in the FDA analysis. Other secondary endpoints, dealing with numerical alterations is seizure rates exhibited statistical significant effects as compared to placebo or trended in the correct direction. The Global evaluations trended toward improvement in the 400 and 600mg doses. Effects of quality of life measures were small and inconsistent.

Another secondary endpoint was the reduction in seizures by seizure type (i.e. simple partial, complex partial and partial secondarily generalized). These data were only presented using descriptive statistics. There was likely insufficient power to draw definitive conclusions. In general both complex partial seizures and partial secondarily generalized all trended in a direction that suggested a therapeutic effect. The effect on simple partial was more inconsistent. No definitive trend was observed, with some studies showing decreases and others increases in seizure activity of drug over placebo. Nothing can be definitively drawn from these data as these seizures were the least frequently observed and the data would be prone to a sampling error.

Dr Massie, the statistical reviewer, confirmed the Sponsor's analysis for all performed studies. Dr Massie also noted that "overall, there was no compelling evidence that the treatment effect varied by gender." He also determined that there was no obvious age dependency for the age range studied (16 to 71 years of age). Considering the limitation of the small size of the non-Caucasian sample size, it was concluded that no obvious racial differences in effect was observed.

This reviwer concludes that both the 200, 400 mg/day dose (divided bid) impart a therapeutic effect in adjunctive treatment of partial seizures. The 600mg/day dose does not appear, on

average, to be superior to the 400 mg dose. The 200 mg dose may, on average, appears to have a smaller therapeutic benefit. However, on an individual basis, dosing will have to be adjusted not only based upon therapeutic benefit but also on tolerability. As will be discussed in the safety section, the 600 mg dose was poorly tolerated.

The Sponsor intends to marke[redacted]ormulations of lacosamide: tablets, intravenous solution [redacted] All pivotal studies were performed using a tablet formulation. Conclusions for efficacy for other formulations are based upon studies demonstrating equivalent bioavailability between those formulations and the tablet formulation. [redacted] Bioequivalence was also demonstrated with the iv infusion solution when such infusions were performed over 30 and 60 minutes. Shorter infusions resulted in higher Cmax values in the formal bioequivalence studies (see Pharmacokinetic section above). b(4)

7 INTEGRATED REVIEW OF SAFETY

This was performed by the Dr. Villalba of the safety Team. The reader is referred to that review and the executive summary in this review..

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This reviwer concludes that both the 200, 400 mg/day dose (divided bid) impart a therapeutic effect in adjunctive treatment of partial seizures. The 600mg/day dose does not appear, on average, to be superior to the 400 mg dose. The 200 mg dose may, on average, appears to have a smaller therapeutic benefit. However, on an individual basis, dosing will have to be adjusted not only based upon therapeutic benefit but also on tolerability. As will be discussed in the safety review, by Dr Villalba, the 600 mg dose was poorly tolerated.

8.2 Drug-Drug Interactions

Se PK.

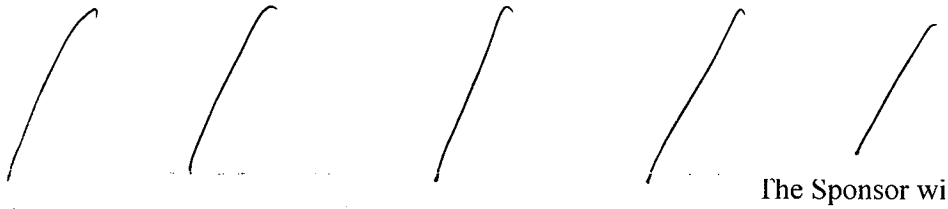
8.3 Special Populations

Based upon efficacy trials, there was no compelling evidence that the treatment effect varied by gender." He also determined that there was no obvious age dependency for the age range studied

(16 to 71 years of age). Considering the limitation of the small size of the non-Caucasian sample size, it was concluded that no obvious racial differences in effect was observed.

The clinical pharmacology reviwer note that studies indicate that while no dose adjustments would be necessary for patients with mild to moderate renal impairment, patients with severe renal failure will require dose reductions. Studies indicate that similar adjustments would be necessary for patients with moderate hepatic impairment. Elderly patients experienced a 20-25% greater exposure when weight was taken into consideration. The clinical pharmacology reviewer felt that although this would not warrant dose adjustment on its own, becasue of increased incidence of impaired hepatic and renal function in this class of patients, some caution should be noted in this population. Although females experienced greater exposure, when weight was factored in this differnce disappeared. This led the clinical pharmacology reviwer to conclude that no adjustment is necessary. There were no racial differences in exposure when adjusted for body weight. Poor CYPC19 metabolizers were examined in a small study. No substantial differnce was noted in the plasma concentrations of the parent drug with extensive metabolizers.

8.4 Pediatrics



b(4)

The Sponsor will be expected to pursue a pediatric indication. The study of pediatric patients over 1 month will be deferred and that under 1 month will be waived, as is the policy of this division.

8.5 Advisory Committee Meeting

None necessary.

8.6 Literature Review

No significant literature.

8.7 Postmarketing Risk Management Plan

There is general agreement in the team that a MedGuide should be distributed for the issue of suicidal ideation, as it will be for other anticonvulsant drugs.

There is some differnce in opinion regarding the issue of a MedGuide for Multiorgan hypersensitivity. Dr Villabla, in her review, notes that "MedGuide may help reduce the risk of serious multiorgan hypersensitivity reactions further." It should, however, be noted that this syndrome has been identified in with many anticonvulsants (indeed it was once referred to as anticonvulsant hypesentivity syndrome) and while it is included in the label of these agents no MedGuide had been adapted. Dr Villabla notes in her review that there is no way, at the present time, to determine if this syndrome is more or less common with this agent as compared to others. For these reasons this CDTL feels a MedGuide is not absolutely necessary. Meetings with Dr. Katz and Dr Temple indicate they concur. and labeling in the Warnings section is recommended.

b(5)

b(5)

8.8 Other Relevant Materials

b(4)

b(4)

9 OVERALL ASSESSMENT

9.1 Conclusions

Lacosamide is considered safe and effective for marketing in adjunctive treatment in epilepsy.

9.2 Recommendation on Regulatory Action

An "Approval" response is recommended for both the tablet and intravenous formulations, with limitations on dosing (see above). b(4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is some differnce in opinion regarding the issue of a MedGuide for Multiorgan hypersensitivity. Dr Villabla, in her review, notes that "MedGuide may help reduce the risk of serious multiorgan hypersensitivity reactions further." It should, however, be noted that this syndrome has been identified in with many anticonvulsants (indeed it was once referred to as anticonvulsant hypesentivity syndrome) and while it is included in the label of these agents no MedGuide had been adapted. Dr Villabla notes in her review that there is no way, at the present time, to determine if this syndrome is more or less common with this agent as compared to others. For these reasons this CDTL feels a MedGuide is not absolutely necessary. Meetings with Dr. Katz and Dr Temple indicate they concur. and labeling in the Warnings section is recommended. b(5)

b(5)

9.3.2 Required Phase 4 Commitments

- Pharm/Tox has recommended: "Further assessment of lacosamide's effect on brain development is needed and that this assessment may be conducted postapproval. Such an assessment should certainly involve dosing in rat throughout the critical periods that correspond to the entire period of human fetal development with, perhaps, direct dosing of the neonate, and, as Dr. Fisher notes, the use of sensitive methods for assessing neurobehavioral function and expanded histopathological examination of the brain. "

- Clinical Pharmacology recommends a phase IV commitment is recommended to "determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19. "

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

See labeling.

9.5 Comments to Applicant

See letter.

REFERENCES

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/s/

Norman Hershkowitz
10/28/2008 12:54:03 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION I

MEMORANDUM

DATE: October 20, 2008

FROM: Ellis F. Unger, M.D., Deputy Director (Acting)
Office of Drug Evaluation I

SUBJECT: Risk Evaluation and Mitigation Strategy (REMS) Requirements for Vimpat (lacosamide) Tablets & Injection (NDA 22-253 & 22-254)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Vimpat (lacosamide) outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs) that includes Vimpat (lacosamide). In reaching this determination, we considered the following:

A. It is not possible to precisely estimate the size of the population likely to use antiepileptic drugs, including Vimpat (lacosamide). The age-adjusted prevalence of epilepsy in developed countries is 4 to 8 per 1,000. It is estimated that approximately three million people in the United States have epilepsy. Many antiepileptic drugs are

also approved for the treatment of other illnesses including bipolar disorder, trigeminal neuralgia, migraine, postherpetic neuralgia, pain from diabetic peripheral neuropathy, and fibromyalgia. The total number of patients receiving a prescription for any of the 11 antiepileptic drugs included in a recent meta-analysis of the risk for suicidal thoughts and behavior with antiepileptic drugs in outpatient retail pharmacies in the United States was over 11 million in 2007.

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy. Many of the deaths in persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, and the underlying condition resulting in seizures. Antiepileptic drugs are also approved for a variety of other treatment indications (Attachment 1). Many of these illnesses are also associated with substantial morbidity and an increased risk of mortality.

C. Antiepileptic drugs have a demonstrated ability to reduce the frequency of seizures when used for treatment of epilepsy. Some antiepileptic drugs also are approved for the treatment of conditions other than epilepsy (Attachment 1 describes approved indications other than epilepsy for the antiepileptic drugs that were studied in the meta-analysis [described below]).

D. Antiepileptic drugs are used as chronic therapy in patients with epilepsy. Duration of treatment may vary for other treatment indications.

E. A known serious risk of antiepileptic drugs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a recent meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 approved AEDs.[1]
In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population. Estimates of the

[1]Statistical review and evaluation: Antiepileptic drugs and suicidality. (Accessed September 24, 2008, at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf.)

incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy. The background incidence of suicide is also estimated as being higher in other conditions for which antiepileptic drugs are indicated, including bipolar disorder. In patients with bipolar disorder, the estimated rate of suicide is 0.40% per year (compared to the international general population average of 0.017% per year); the standardized mortality ratio is estimated to be 22.

F. Vimpat (lacosamide) is a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Vimpat (lacosamide) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Vimpat (lacosamide). FDA has determined that Vimpat (lacosamide), has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Vimpat (lacosamide). In addition, patient labeling could help prevent serious adverse effects related to the use of Vimpat (lacosamide)
The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Attachment 1

FDA-approved non-epilepsy treatment indications of antiepileptic drugs (AEDs) with data in the FDA analysis of AEDs and suicidality

Drug	Treatment Indications
Carbamazepine	trigeminal neuralgia
Gabapentin	postherpetic neuralgia
Lamotrigine	bipolar disorder (maintenance)
Pregabalin	neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
Topiramate	migraine
Divalproex sodium	mania, migraine

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/s/

Jackie Ware
10/28/2008 07:49:50 PM
CSO

Ellis Unger
10/28/2008 07:51:53 PM
MEDICAL OFFICER

CLINICAL REVIEW
Addendum

Application Type	NDA 22-253, 22-254
Submission Number	000
Letter Date	September 28, 2007
Major amendment	July 16, 2008
PDUFA Goal Date	October 28, 2008
Reviewer Name	Lourdes Villalba, M.D.
Addendum Date	September 19, 2008
Established Name	Lacosamide
(Proposed) Trade Name	VIMPAT
Therapeutic Class	Anticonvulsant
Applicant	Schwartz Biosciences
Priority Designation	S
Dosing Regimen	200- mg/day, oral tablet and IV solution for infusion
Indication	As adjunctive therapy in subjects with partial-onset seizures
Intended Population	16 years and above

1. EXECUTIVE SUMMARY

This is an addendum to the June 6, 2008 safety review of NDA 21-253 (Vimpat™). This document includes the review of informational requests that were pending at the time of the original review, as well as additional analyses of potential cases of multiorgan hypersensitivity reactions in the lacosamide database (Major Amendment dated August 14, 2008, received on August 18, 2008). Other adverse reactions have been addressed in the original review.

The sponsor identified 60 potential cases of multiorgan hypersensitivity (57 with lacosamide and 3 with placebo) among 4041 subjects included in the analysis (cut-off date of June 12, 2007). Upon review of the cases, the sponsor concluded that there were no cases of multiorgan hypersensitivity. In my opinion, there were no new cases of serious multiorgan hypersensitivity, however, the case of hepatitis/nephritis identified in the original application remains a case of a drug-induced delayed multiorgan hypersensitivity reaction. The lack of substantial information related to the patient who died of myocarditis and hepatitis precludes a definitive diagnosis in this case.

Multiorgan hypersensitivity reactions are rare but potentially fatal. They are known to occur with most anticonvulsants as well as other drugs, such as sulfonamides and allopurinol. DRESS (another name used to describe these reactions) has been reported to occur in 1/10,000 subjects exposed to anticonvulsants. At this time it is unclear whether lacosamide is associated with a greater risk than other anticonvulsants. Without an adequate comparative database it is impossible to draw definitive conclusions. Part of the problem is the lack of validated definition and the inconsistency in coding and reporting of these events.

Multiorgan hypersensitivity should be described under the WARNINGS and PRECAUTIONS section of labeling. A Risk Evaluation and Mitigation Strategy might be helpful to better characterize and reduce the risk of serious multiorgan hypersensitivity reactions with lacosamide. b(5)

2. BACKGROUND

The primary review of the safety of lacosamide (LCM) for the treatment of partial onset seizures was completed on June 6, 2008. Recommendations included approval of a maximum dose of 400 mg daily, with a REMS that addressed cardiac disorders, suicidality, and multi-organ hypersensitivity reactions. The current document is an addendum to the June 6, 2008 safety review and includes the following: b(5)

- Review of information pending at the time of the June 6, 2008 review
- Errata from the June 6, 2008 review
- Follow up on case of hepatitis and nephritis submitted with the original submission

- Follow up of one fatal case of myocarditis and hepatitis submitted as part of the SUR
- Follow up on potential cases of multi-organ hypersensitivity reactions submitted in response to an FDA informational requests of June 12, 2008 (major amendment received July 16, 2008) and July 25, 2008 (received August 22, 2008).

3. REVIEW

3.1 Review of information pending at the time of the June 6, 2008 review

To evaluate whether the exclusion criteria - particularly those pertaining to the use of concomitant medications and concomitant diseases that affect the heart conduction system- had substantially impacted the generalizability of the results of the partial onset seizure studies, the DNP asked the sponsor to provide the number and reasons for not randomizing patients to the epilepsy studies (SP667, SP754 and SP755). The sponsor's response was received on June 13, 2008 (s0014).

Out of 1682 subjects screened for the epilepsy studies, 371 (22%) were not randomized because they either did not meet eligibility criteria at screening or terminated during the baseline phase. Of the subjects screened, approximately 9% (149/1682) did not fulfill baseline diagnosis, seizure activity or concomitant antiepileptic treatment requirements; 5% (82/1682) dropped out during the 8-week run-in period (withdrew consent, adverse event, unsatisfactory compliance or lost to follow up); and 9% (157/1682) fulfilled one or more of the exclusion criteria. A table summarizing the reasons for exclusion from the epilepsy trials is presented in Appendix 1.

Overall, 2% (18/1682) of the screened subjects were not enrolled because they were taking prohibited medications, 2% had abnormal liver tests (ALT/ALT > 2xULN), 2% had an abnormal ECG (mostly prolonged QTc) and 1% had some underlying medical condition that warranted exclusion (no details provided). Additionally, a few subjects were not included because they were taking vigabatrin (7 [0.4%], which is not currently marketed in the U.S.) or felbamate (2 [0.1%]).

COMMENT: The population excluded from these epilepsy studies does not appear to be very different from that in studies with other antiepileptic drugs. b(5)

The labeling should note [redacted]

3.2 Errata from the June 6, 2008 review

Page 75 of the June 6, 2008 review states that the rate of first degree AV block during the epilepsy studies in the lacosamide group was 4.2% on lacosamide, versus none on placebo. The correct rate is 0.42% (4/944) for the lacosamide group, versus 0 on placebo (0/364).

3.3 Follow up on one case of hepatitis and nephritis in a healthy volunteer

Subject 588/8061 was described in detail in my review dated June 6, 2008, under section 7.1.2, Serious Adverse Events in Phase 1 studies with LCM oral formulation. The sponsor had stated that on [redacted], the day that the subject presented to the emergency room with fatigue, elevated transaminases dark urine and proteinuria, bilirubin had not been measured. b(6)

On July 31, 2008, the sponsor submitted a certified translation of the [redacted] emergency room (ER) visit, stating that blood total bilirubin was 16 (no units provided). Other laboratory values included hematocrit, 47; leukocytes 8.7; creatinine 116; uric acid 456; total protein 70; sodium 145 and potassium 4.5 (all without units). Urinalysis showed 2+ protein, negative bilirubin, granulated cylinders and urates. A separate document certifies that the units used by the laboratory for creatinine, uric acid sodium, potassium and bilirubin were µmol/L. The normal range for BR was 0-22 µmol/L. All laboratory evaluations in this patient were within normal values.[1] b(6)

In addition to the symptoms described above, the report states that on [redacted] the subject had edema of both arms. A diagnosis of toxic hepatitis and nephritis was made in the ER. Subsequently (not included in the ER report) an immunologist who evaluated the subject concluded that this was a case of drug induced delayed hypersensitivity. Of note, eosinophil count was not done in the ER. b(6)

> *COMMENT: At the time of the event of hepatitis and nephritis, diagnosed as a possible drug induced delayed hypersensitivity reaction, the subject's total bilirubin was 16 µmol/L, which is within normal values.*

LCM at doses of 200 to 600 mg daily is associated slight transaminase (AST/ALT) and GGT elevation, as compared to placebo (2.4% on LCM, vs. 1.1% on placebo in EP S1). The rate of ALT/AST ≥3x ULN in EP S1 was 0.7% and 0% in the LCM and placebo groups, respectively. No patient presented transaminase elevation >5 x ULN and jaundice in this database.

Information about increase in transaminase should be included in the laboratory results section. The potential for hypersensitivity-mediated drug induced hepatitis should be mentioned along with multiorgan hypersensitivity reactions. [redacted] does not appear to be warranted at this point. b(5)

3.4 Follow up of a fatal case of myocarditis and hepatitis submitted with the SUR.

Page 28 of my June 6, 2008 review mentions a fatal case of myocarditis and hepatitis (Subject # 830/111201). The full narrative of this case as presented by the sponsor in the original SUR is as follows:

[1] Normal range values were submitted in a separate document on August 11, 2008.

SUBJECT SP830/111201

Open-label:
Lacosamide

DER No.:
N/A

Drug and Actual Dose at AE Onset:
Lacosamide 600mg/day

Investigator: b(4)

Serious Adverse Event Leading to Death (coded term [reported term]):
Myocarditis (toxic damage of myocardium)

Other Significant Adverse Event (coded term [reported term]):
Sinus tachycardia (sinus tachycardia [ECG finding])

Subject 111201 was a 39-year-old white male at the time of enrollment. His medical history included radius fracture (2005 and 1971), rib fracture (2005), diabetes mellitus insulin-dependent (2003), hepatitis A (1985), pneumonia (1977). He entered the open-label SP830 trial on 18 Apr 2005 with painful, distal diabetic neuropathy and started titration with lacosamide 100mg/day on 04 May 2005. At the time of the adverse event (AE) of sinus tachycardia (sinus tachycardia [ECG finding]), the subject was taking lacosamide 600mg/day and had been at this level for 8 days. At the time of the AE of myocarditis, the subject was not taking trial medication and had taken his last dose of lacosamide 400mg/day on 18 Aug 2006.

On 28 Jun 2005, during the Titration Phase, the subject experienced sinus tachycardia of mild intensity. His vital sign measurements were recorded as pulse of 110bpm and blood pressure of 130/80mmHg. An electrocardiogram showed a heart rate of 110bpm and normal intervals. Trial medication was unchanged and no therapeutic measures were administered to treat the event. The sinus tachycardia was reported to be resolved on 27 Jul 2005.

b(6)

On ——, the subject died due to myocarditis (toxic damage of myocardium) of severe intensity. At the time of death, the subject was also suffering from alcoholic intoxication and toxic damage of the liver (no further information regarding this diagnosis is available). The investigator noted that there subject had no history of alcohol abuse and the date of onset of the toxic damage of the liver is unknown. No further information available.

Concomitant medications at the onset of the sinus tachycardia included insulin glargine 30IU/day, soluble human insulin 36IU as needed, and fosinopril 40mg/day.

The sinus tachycardia was reported as a nonserious AE and the myocarditis was reported as a serious AE (category: results in death). The investigator considered the sinus tachycardia to be possibly related to trial medication. The myocarditis was considered to be not related to trial medication and highly probably related to other factors (no additional causality information is available).

Reviewer's comment: The information about dosing at the time of the fatal event is incorrect. The date of last lacosamide dosing is unknown. The patient might have stopped and re-started LCM without notifying the investigator.

Of note, the case report form states that the date of the last dose is unknown. This was confirmed by the study site investigator. Lacosamide 400 mg daily was last dispensed on August 18, 2006, to cover three months of treatment. The patient died on —— b(6)
—— There is no available information from hospital records or autopsy report.

COMMENT: Given the report of myocarditis and hepatitis in a patient taking an investigational aromatic anticonvulsant drug in addition to one case of hepatitis and nephritis consistent with drug hypersensitivity in a healthy volunteer who received this drug in a phase 1 study, I am concerned about the possibility that the case if myocarditis and hepatitis could be a case of multi-organ hypersensitivity.

I acknowledge that the case would be unusual because the myocarditis/hepatitis occurred one year and 4 months into the trial. However, there is very limited information about the case, whether the patient stopped and re-started lacosamide; whether there was eosinophilia, rash, fever or other major organ involvement; whether there was any kind of work up for etiologic factors done at the time of the diagnosis and whether there were pathology results.

The family reported the cause of death as "toxic myocarditis" and "alcoholic toxic hepatitis", but the investigator noted that the patient did not have a history of alcohol abuse. Moreover, it is unclear whether the patient had an autopsy or not. The sponsor states that the family declined to provide any additional information. No further information is available for this patient.

Data are insufficient to completely rule out a case of multiorgan hypersensitivity.

3.5 Follow up on potential cases of multi-organ hypersensitivity reactions submitted in response to an informational request.

3.5.1 Background

Because of the case of hepatitis/nephritis in a healthy volunteer and the fatal case of myocarditis and hepatitis in subjects who took lacosamide, the DNP requested additional analyses to evaluate the possibility of multiorgan hypersensitivity reactions with this drug.

Multiorgan hypersensitivity reactions are delayed idiosyncratic drug reactions, characterized by systemic involvement. The syndrome has been recognized for many years but has been reported under different names such as drug [e.g allopurinol, dapsone, anticonvulsant] hypersensitivity syndrome, hypersensitivity syndrome ("HS") or simply "hypersensitivity". Most recently, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)[2], and Drug-Induced Delayed Multiorgan Hypersensitivity Syndrome (DIDMOHS) [3] have been proposed. Because skin lesions are not a constant feature, Bocquet et al. (the authors who originally proposed the name DRESS), have recently suggested that the R in DRESS could be used more properly to indicate "reaction."[4] They point out that Toxic Epidermic Necrolysis (TEN) and Steven Johnson syndrome (SJS) are also associated with systemic involvement, but have different pathologic findings and should not be lumped together with DRESS as part of one "hypersensitivity syndrome" entity.

DRESS has been estimated to occur in about 1 in 10,000 exposures with drugs such as antiepileptics and sulfonamides.[4] It usually begins 2-6 weeks after the first drug use (later than most other skin reactions). The literature cites phenytoin, carbamazepine and phenobarbital as frequent culprits of the anticonvulsant hypersensitivity syndrome. Multi-organ hypersensitivity has also been described with Lamictal (lamotrigine) and Trileptal (oxcarbazepine), and is mentioned in the respective labelings. The anticonvulsant hypersensitivity syndrome has not been reported in the literature during monotherapy with topiramate, gabapentin or levetiracetam, and is reported rarely with valproic acid.[5]

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[2] Bocquet H, Bagot M, Roujeau J-C. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms-DRESS). Semin Cutan Med Surg. 1996;15:250-257.
[3] Sontheimer, RD, Houpt, KR. DIDMOHS: a proposed consensus nomenclature for the drug-induced delayed multiorgan hypersensitivity syndrome. Archives of Derm. 1998;134(7):874-876 (Correspondence).
[4] Bocquet, H; Bagot, M, Roujeau, JC. Archives of Derm. 1998;134(7):874-876 (Correspondence).
[5] Krauss, G. Current understanding of delayed anticonvulsant hypersensitivity reactions. Epilepsy Currents. 2006(6):33-37.

However, a recent review of postmarketing reports of DRESS in AERS found reports with all anticonvulsants, except topiramate and levetiracetam.[6] (See Appendix 2.)

DRESS is characterized by severe systemic disease in some patients, such as fever, lymphadenopathy, various forms of long-lasting rash and visceral involvement (e.g. hepatitis, nephritis, myocarditis, pericarditis, pneumonitis). Blood alterations are characteristically associated with DRESS, with eosinophilia >1500 in 60-70% of cases, often associated with lymphocytosis and atypical basophil lymphocytes[7] or monocytosis in up to 40% of cases.[3]

The syndrome is potentially life-threatening. The mortality rate of DRESS is estimated at near 10%. In other cases, recovery is usually total. Rash and hepatitis may persist for weeks; some cases persist for months, despite withdrawal of the causative agent. [8] There may also be persistent intolerance to chemically distinct drugs, leading to flare-up reactions months after the initiating drug therapy is stopped.[9]

The pathogenesis of the disorder has not yet been identified. Activated T cells are often found in the circulation, similar to patients with acute HIV or generalized herpesvirus infections. A role of viral co-infection is suspected. The clinical picture resembles that of a generalized viral infection, such as an acute EBV infection, but it is distinguished by prominent eosinophilia. Recently it has been shown that human herpesvirus-6 DNA can be found in many patients with this syndrome during the 3rd or 4th week of the disease, but not before, followed by an increase in antibodies to human herpesvirus-6. Other reports document reactivation of CMV infection. Thus, **drug-induced massive immune stimulation** may somehow lead to a loss of control of these herpesviruses, which subsequently replicate and contribute to the chronic course and persistent drug intolerance.[9]

Drug induced hepatitis, nephritis, interstitial lung disease, pancreatitis or isolated fever can also be the only symptom of a drug allergy. Sometimes eosinophilia helps to distinguish a peculiar drug reaction from other diseases and suggests a T-cell mediated process, since these cells are the main source of the eosinophil-stimulating cytokine IL-5.[9]

Given the two cases described above, the DNP asked Schwartz to conduct a formal review of their clinical database to identify possible cases of multi-organ hypersensitivity. The sponsor's response was received on July 16, 2008 and updated on August 18, 2008.

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[6] WebVDME search of AERS conducted on 9/22/08 for the preferred term DRESS only.
[7] Roujeau, JC. Clinical heterogeneity of drug hypersensitivity. Toxicology 209 (2005) 123-129.
[8] Ghislain and Roujeau, Treatment of severe drug reactions. Dermatology Online Journal, Vol 8, Number 1.
[9] Pichler, W. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139:683-693

3.5.2 Review of the sponsor's response to additional request for information

3.5.2.1 Sponsor's Methodology

Because of the lack of a widely accepted case definition for the identification of multiorgan hypersensitivity reactions, the FDA initially advised the sponsor to look for "internal organ involvement (ie, hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least two of the following: fever, rash, lymphadenopathy." Such approach had been previously accepted by the Agency for identification of potential multiorgan hypersensitivity reactions with Provigil and Nuvigil.[10]

On June 12, 2008, during a teleconference between FDA and the sponsor, Schwarz agreed to conduct such analysis. Moreover, the sponsor agreed to include subjects with one instead of two out of the three (fever, rash, lymphadenopathy) terms.

Trials included in the sponsor's review were all Phase 1 LCM trials, all oral and intravenous Phase 2 and 3 LCM trials in subjects with partial-onset seizures, and all oral Phase 2 and 3 LCM trials in subjects with neuropathic pain (ie, diabetic neuropathic pain, post-herpetic neuralgia, and neuropathic pain of mixed origin), with a cut-off date used for the 120-day Safety Update.

A subject was identified as a potential multi-organ hypersensitivity case if he/she was reported to experience an adverse event (AE) or have a laboratory value related to internal organ involvement (Group A) and at least one AE suggestive of fever, rash, or lymphadenopathy (Group B). The onset of the Group A AE and the Group B AE was required to occur within 28 days of each other in order for a case of interest to be identified. The list of terms included in Group A and Group B are presented in Tables 1 and 2, respectively.

[10] Dr. Bryan Wilson's review. December 21, 2006

Table 1. Adverse events and laboratory value criteria suggestive of internal organ involvement (Group A) in subjects treated with oral or IV LCM.

MedDRA® SOC/Preferred term
Blood and lymphatic system disorders
Eosinophilia
Granulocytopenia
Leukopenia
Neutropenia
Pancytopenia
Thrombocytopenia
Gastrointestinal disorders
Colitis
Pancreatitis
Pancreatitis acute
Enterocolitis
Hepatobiliary disorders
Hepatic Function Abnormal
Hepatotoxicity
Investigations
Alanine Aminotransferase Increased
Lipase increased
Aspartate Aminotransferase Increased
Eosinophil Count Increased
Granulocyte Count Decreased
Hepatic Enzyme Abnormal
Hepatic Enzyme Increased
Liver Function Test Abnormal
Neutrophil Count Decreased
Platelet Count Decreased
Musculoskeletal and connective tissue disorders
Arthritis
Myositis
Polyarthritis
Renal and urinary disorders
Nephropathy toxic
Laboratory value criteria
Eosinophils % ≥10%
Eosinophils absolute ≥0.5G/L
Neutrophils absolute <1.5G/L
Platelets ≤100G/L
ALT ≥2xULN
AST ≥2xULN

ALT=alanine aminotransferase;
AST=aspartate aminotranseras;
iv=intravenous;
LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities;
SOC=system organ class;
ULN=upper limit of normal
G/L = giga units per liter or 10 to the 9th power per liter

Source: Table in Pg. 3 of July 16 response

Table 2. Adverse events suggestive of fever, rash or lymphadenopathy (Group B) in subjects treated with oral or IV LCM

MedDRA® SOC/Preferred term
Blood and lymphatic system disorders
Lymphadenitis
Lymphadenopathy
Lymphadenopathy Mediastinal
General disorders and administration site conditions
Pyrexia
Skin and subcutaneous tissue disorders
Dermatitis Allergic
Rash
Rash Erythematous
Rash Generalised
Rash Macular
Rash Macular-Papular
Rash Morbilliform
Rash Papular
Rash Pruritic
Rash Psoriaform
Drug Eruption
Uriticaria

Source: Table in page 5 of July 16 response.

Review of the terms used in the sponsor's search indicated that several relevant terms were missing from the analysis. For instance, under Renal and urinary disorders, only "nephropathy toxic" was included. There were no terms such as nephritis, renal insufficiency or proteinuria.

On July 25, 2008, the DNP suggested that in addition to the originally proposed terms the following terms be included in groups Group A and B, (Tables 3 and 4, respectively):

Table 3. Adverse events and laboratory value criteria suggestive of internal organ involvement (Group A) in lacosamide studies

MedDRA SOC	MedDRA Preferred Term	
	Proposed by Schwartz	*Additional FDA terms (MedDRA 11.0)*
Blood and lymphatic system disorders		
	Eosinophilia Granulocytopenia Leukopenia Neutropenia Pancytopenia Thrombocytopenia	*lymphocytosis, atypical lymphocytosis, monocytosis, mononucleosis, blood disorder, splenomegaly, hepatosplenomegaly, splenitis, eosinophilic bronchitis/cellulitis/colitis/ cystitis/myocarditis/esophagitis/pneumonia,*

		basophilia, white blood cell disorder, hepatic infiltration eosinophilic.
Gastrointestinal disorders		
	Colitis Pancreatitis Pancreatitis acute Enterocolitis	
Hepatobiliary disorders		
	Hepatic function abnormal Hepatotoxicity	*jaundice, hepatitis, hepatitis toxic, hepatic failure, hepatomegaly*
Immune system disorders		
		hypersensitivity, Type IV hypersensitivity reaction
Investigations		
	ALT increased Lipase increased AST increased Eosinophil count ↑ Granulocyte count ↓ Hepatic enzyme abnormal Hepatic enzyme ↑ Liver function test abnormal Neutrophil count ↓ Platelet count ↓	*Lymphocyte count increased, leukocyte count increased, monocyte count increased, basophil count increased, white blood cell morphology abnormal, biopsy liver abnormal, biopsy kidney abnormal, biopsy lung abnormal, immunology test abnormal, biopsy skin abnormal, urinary casts present*
Musculoskeletal and connective tissue disorders		
	Arthritis Myositis Polyarthritis	*joint swelling, joint warmth, arthralgia, arthropathy*
Neoplasm benign, malignant and unspecified		
		pseudolymphoma
Renal and urinary disorders		
	Nephropathy toxic	*nephritis, renal toxicity, renal insufficiency, renal failure, proteinuria, hematuria, oliguria, nephrotic syndrome, nephritis allergic, nephritic syndrome, nephritis interstitial*
Respiratory, thoracic and mediastinal disorders		
		interstitial lung disease, pneumonitis, alveolitis, alveolitis allergic
Laboratory value criteria		
	Eosinophils % ≥ 10% Eosinophils absolute ≥ 0.5G/L Neutrophils absolute < 1.5G/L Platelets ≤ 100G/L ALT ≥ 2xULN, AST≥ 2xULN	

Table 4. Adverse events and laboratory value criteria suggestive of fever, rash or lymphadenopathy (Group B) in lacosamide trials.

MedDRA SOC	MedDRA Preferred Term	
	Proposed by Schwartz	*Additional FDA terms (MedDRA 11.0)*
Blood and lymphatic system disorders		
	Lymphadenitis Lymphadenopathy Lymphadenopathy mediastinal	
General disorders and administration site conditions		
	Pyrexia	
Skin and Subcutaneous tissue disorders		
	Dermatitis allergic Rash Rash erythematous Rash generalized Rash macular Rash macular-papular Rash morbilliform Rash papular Rash pruritic Rash psoriaform Drug eruption Urticaria	*Drug Rash with Eosinophilia and Systemic Symptoms,* *toxic skin eruption, exfoliative rash, skin exfoliation, rash vesicular.*

COMMENT: There is no validated case definition for multiorgan hypersensitivity. We had previously agreed with the sponsor to evaluate cases with at least one AE from Group A and one from Group B. The addition of more terms will potentially increase the sensitivity but will further decrease the specificity of this search. On the other hand, this is not an exhaustive list. The FDA request avoided including terms such as nausea, vomiting, headache, fatigue or abdominal pain, although some of them might in fact be part of a systemic hypersensitivity reaction. [11] *This is an exploratory analysis. A good case definition would require consensus and validation among experts.*

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[11] As an example of another approach that has been used by the Agency to identify hypersensitivity reactions – although not called multiorgan hypersensitivity-, the labeling for abacavir (Ziegen™) (http://www.fda.gov/cder/foi/label/2008/020977s017,020978s020lbl.pdf) recommends the presence of AEs in two out of five AE categories as follows

Group 1: Fever

Group 2: Rash

Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

The abacavir approach includes many terms that are commonly associated with LCM use and unlikely to be due to drug hypersensitivity.

On August 14, 2008 (received August 22, 2008), the sponsor submitted a new analysis of potential multiorgan hypersensitivity reactions incorporating the terms requested by the DNP on July 25, 2008. The sponsor mapped the terms requested by FDA to the version used in their NDA submission (MedDRA 9.1). A final list of events included in the updated analysis is presented in Appendices 3 and 4 of this review.

3.5.2.2 Summary of results of the July 16, 2008 analysis

The analysis submitted on July 16, 2008 identified **50** subjects with reported terms that could potentially represent a multiorgan hypersensitivity reaction among 4605 subjects included in the search (4011 who received LCM, 488 who received placebo and 106 who did not receive either).[12] Out of the 50 subjects, **27** (25 on LCM, two on placebo) were identified using the Division's originally suggested algorithm and **23** (22 on LCM and one on placebo) using a complementary approach that evaluated subjects who had any of the following medically important AEs: hypersensitivity, anaphylactic reaction, myocarditis or hepatitis, regardless of the presence of fever, rash or lymphadenopathy.

> *COMMENT: The cases previously identified by the DNP as potential multiorgan hypersensitivity reactions were not captured with the DNP suggested approach, as none was reported to have fever, rash or lymphadenopathy, but were captured by the sponsor's alternative approach.*

3.5.2.3 Summary of results of the August 14, 2008 analysis

The updated analysis of August 14, 2008, identified **60** subjects with reported terms that could potentially represent a multiorgan hypersensitivity reaction among 4605 subjects included in the search, **39** of whom were identified using the Division's suggested algorithm (37 on LCM, two on placebo) and **21** (20 on LCM and one on placebo) using the sponsor's complementary approach described above.[13] Overall, the crude rate was 1.4% among subjects receiving LCM (57/4011) and 0.6% among subjects receiving placebo (3/488).

> *COMMENT: The updated analysis identified 10 additional cases, most of them related to the musculoskeletal system (arthritis, arthralgia, joint swelling).*

[12] Denominators were provided at the FDA request, on August 1, 2008. Some subjects enrolled in Phase 1 trials and did not receive LCM or placebo (eg, subjects receiving moxifloxacin).
[13] Two cases identified in the July 16 submission were captured by the FDA approach in the August 18, 2008 submission.

3.5.2.3.1 Review of cases identified by the DNP suggested approach

The sponsor concluded that none of the 57 cases identified by the DNP approach was a case of multiorgan hypersensitivity. Upon review of individual cases, I agree that there are no cases of serious, full blown multiorgan hypersensitivity, however, while some cases are clearly not multiorgan hypersensitivity reactions, others are consistent with a mild or aborted reaction and many provide insufficient information to make any kind of diagnosis. A summary table of the cases submitted on 08/18/08 is presented in Appendix 5 of this review. The FDA reviewer's clinical impression on these cases is summarized in the following table.

Table 5. FDA review of cases with terms suggestive of a potential multiorgan hypersensitivity reaction in LCM studies. Cases identified with DNP suggested approach.

Subject ID	FDA Comments
Consistent with early, mild or aborted multiorgan hypersensitivity reaction	
836000010, 746141104	Subject had at least two AE that appeared to be drug related. Drug was discontinued early. For narratives, see text.
Insufficient information	
768109807, 6111024, 5880008053, 66711005-80186, 640082076, 615010052, 768109712	Poor description or poor follow up. For examples, see text.
Unlikely to be a multiorgan hypersensitivity reaction	
641080204, 641080501, 607001454, 615011028, 66710102-80116, 66711801-80028, 75416106, 755100804-80254* *7552410I*, 76012201, 760012402, 756016106, 614001807, 665010093, 742012705*, 42016303, 745114718, 745174208, 745175804, 745176209, 768108312-80420, 768111003, 768112501-80226, 830105613, 768109109, 830102604	Subject had at least one AE that appeared to be drug related (e.g. rash) but other components of the "multiorgan" case either preceded the use of LCM or had other potential explanation.
66611814-80284, 667013511, 75612005, 757150001, 745111802	Subject had at least two of these AEs while taking LCM but one or more events resolved despite continuous LCM therapy.

The following cases warrant further discussion, because they might represent an early, mild or aborted case of multiorgan hypersensitivity:

- **Subject 836000010** was a 27-year-old white male healthy volunteer who presented **rash** and **elevated transaminases** while on lacosamide. He started LCM on 27 Oct 1998 at a dose of 200mg/day. On 31 Oct 1998, on day #5 of exposure to trial medication, the subject developed a moderate rash on his forearm followed by a mild rash on the inner aspect of his right thigh, which was treated with hydrocortisone 1% cream. On 02 Nov 1998, on day #7 of exposure to trial medication (the last day of a 7-day trial), the subject experienced ALT increased of mild intensity. ALT was 59 IU/L (1.5 x ULN, from 22 at baseline; normal range 8 to 39U/L). His

AST was normal. No therapeutic measures were reported to treat the event. The event of rash was reported to be resolved on 07 Nov (five days after stopping study drug) and elevated ALT was reported to be resolved on 09 Nov 1998 (seven days after stopping study drug). There is no available CBC and differential cell count after baseline.

COMMENT: This case is consistent with mild drug hypersensitivity with mild skin rash and liver toxicity on day 5 of a 7-day study. Eosinophil count at that time is not available. LCM was stopped because the treatment was completed. It is conceivable that he could have gotten worse if he continued with LCM treatment. There was no re-challenge.

- **Subject 746/14104:** skin rash, liver enzymes increased, elevated eosinophils. This patient was a 77-year-old white male with a medical history of diabetes and drug hypersensitivity (in 1980 and later at an unknown date, to unknown drug). He entered the double-blind SP743 trial with painful diabetic neuropathy and was randomized to LCM 600mg/day. He started LCM on 19 August, 2004. He withdrew early because of dizziness and weakness in both legs on day #30. Subsequently he entered the open-label SP746 trial and began dosing with LCM 100mg/day on 22 Nov 2004.

  On 05 Jan 2005, on day #44 of the OL study he developed a mild skin rash (no further description available). At that time he was taking LCM 300mg/day. The rash was treated with chlorpheniramine 4 mg as needed. The event was reported as resolved 2 days later.

  On 11 Jan 2005, on day #50 of the OL study, still on LCM 300, he presented liver enzymes increased (>7x ULN) and bilirubin increased, that led to withdrawal. The last dose of trial medication was taken on 13 Jan 2005. On 7 Feb 2005, transaminases, ALP and bilirubin were down to normal range, although GGT was still 3xULN. Results are summarized as follows:

Laboratory values for Subject 14104

Date	Lacosamide dose (mg/day)	ALT (normal range: 0-41U/L)	AST (normal range: 0-38U/L)	ALP (normal range: 56-119U/L)	GGT (normal range: 11-49 U/L)	Total Bilirubin (normal range 0.18-1.11 mg/dL)
22 Nov 2004	100	19	24	86	29	0.702
16 Dec 2004	300	16	20	81	31	0.760
11 Jan 2005	300	287H	310H	141H	550H	1.345H
14 Jan 2005	N/A	83H	32	125H	351H	0.760
07 Feb 2005	N/A	21	22	96	93H	0.702

ALP= alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gammaglutamyl transpeptidase; NA=not applicable. Values marked as H were flagged as such in trial data listings. N/A: not applicable.

On 14 Jan 2005 his eosinophil percentage was 7.8% (normal range 1 to 6%). The baseline eosinophil value was 6.0%. The value was intermittently above the normal range during the trial.

Concomitant medications at the onset of both AEs included finasteride, lansoprazole, insulin humulin, nitroglycerin as needed, senna, cetirizine, ispaghula husk 1sachet/day, atenolol, alfuzosin, domperidone and paracetamol as needed.

At the time of liver enzymes increased, the subject informed the investigator that he had been diagnosed with pleurisy on 22 Dec 2004, and had started treatment with oxytetracycline 2000mg/day. It is unclear if he was still taking the medication at the time of the elevated transaminases.

COMMENT: The case is consisted with lacosamide-induced liver toxicity (ALT/AST and GGT >7x ULN, and doubling of bilirubin) within two months of starting lacosamide. The case is confounded by the use of oxytetracycline and paracetamol (PRN) for an unknown duration for "pleurisy", however, it is unlikely that he would be taking them for 3 weeks (December 22, when it was diagnosed to January 11, when transaminases were found to be elevated). Moreover, transaminases and bilirubin started to decrease immediately after lacosamide discontinuation (positive dechallenge). The liver toxicity along with the rash and eosinophilia could be part of a multiorgan hypersensitivity reaction. It is unclear whether the pleurisy was infectious or non-infectious, and what tests the patient had at the time of the diagnosis.

The following case is unlikely to represent multiorgan hypersensitivity but there is insufficient information about the case.

- **Subject 588/8053** was a 35-year-old white male healthy volunteer randomized to LCM 1000mg/day on 10 Oct 2000. At the time of the AE of joint swelling and the three AEs of rash pruritic, the subject was taking lacosamide 1000mg/day. Study 588 was a placebo-controlled, 16-day oral capsule study.

  On 10 Oct 2000, 20-30 minutes after the subject took his first dose of LCM 500 mg, the subject experienced dizziness, somnolence, pressure feeling in ears, paresthesia (reported as tingling sensation in lips, back of neck), and fatigue. No therapeutic measures were administered to treat any of the events described above. They resolved within a few hours. These non-serious events were also reported several times during the trial.

  On 15 Oct 2000, on day #6, while taking LCM 1000mg/day, the subject experienced joint swelling (pain and swelling of the left knee) of moderate intensity. The swelling of the left knee was treated with heparin ointment on 17 Oct 2000. The joint swelling had not resolved at the last time of reporting. The subject's eosinophils as well as other laboratory values were within the normal range throughout the trial.

  On 18 Oct 2000, 19 and 20 he experienced rash (rash, itching of neck, shoulders and face) of mild intensity which resolved the same day each time. No treatment was reported for these AEs. The rash appeared again on October 26, one day after LCM was discontinued, and resolved on October 27, 2000.

  COMMENT: The recurrent pruritic rash was likely drug related. A single swollen joint within 5-10 days of starting treatment would be unlikely to be a drug reaction. However, there is little information about the swollen joint. There is no

mention of previous trauma. No XRays, blood tests (uric acid, ANA, RF) or fluid analyses (cytology, crystals, cultures) were done that could identify its etiology. This could potentially be an immune-mediated synovitis. Moreover, the study lasted only 16 days. Swelling and recurrent rash were ongoing at the end of study and there is no follow up information about the outcome of the joint swelling, rash or laboratories. Of note, this is the same study of high-dose LCM capsule formulation in which a subject presented hepatitis/nephritis more than a week after stopping LCM.

Other cases under the category of "insufficient information" include reports of "hypersensitivity" without any details about the reaction, and cases in which some of the terms did not appear to be hypersensitivity but the subject discontinued from the trial for unclear reasons.

3.5.2.4 Review of cases identified by the sponsor's alternative approach (August 14, 2008)

Using the following selected MedDRA preferred terms of medical importance: hepatitis, myocarditis, hypersensitivity and anaphylactic reactions, the sponsor identified **21** potential cases of multiorgan hypersensitivity. A summary of these cases is presented in Appendix 6 of this review. The sponsor concluded that none of the cases was consistent with true drug induced multiorgan hypersensitivity. The FDA reviewer agrees with the sponsor assessment in most cases.

The majority of cases coded as hypersensitivity actually referred to seasonal allergies; some cases appeared to be associated with the use of other drugs known to cause hypersensitivity (e.g. naproxen); one case was associated with mild lymphocytosis, but both the hypersensitivity ("allergic reaction/generalized swelling) and the lymphocytosis resolved without drug discontinuation and are therefore unlikely to be drug related.

Two cases captured with this approach, **Subject SP588/8061** (hepatitis/nephritis in healthy volunteer) and **SP 830/111201** (myocarditis and toxic hepatitis) have been discussed in detail under section 1.3 and 1.4, of this review, respectively. The FDA reviewer continues to believe that the case of hepatitis/nephritis is a case of multiorgan hypersensitivity. The case of myocarditis/hepatitis is not inconsistent with multiorgan hypersensitivity, but there is too limited information to support the diagnosis.

4. CONCLUSIONS AND RECOMMENDATIONS FOR REGULATORY ACTION

4.1 The population excluded from the lacosamide epilepsy studies does not appear to be very different from that in studies with other antiepileptic drugs. b(5)

The labeling [redacted]

4.2 Analyses submitted July 16 and August 14, 2008 did not provide new cases of full blown multiorgan hypersensitivity. There were two cases of elevated transaminases and rash, without fever or lymphadenopathy that may represent a mild or early multiorgan hypersensitivity reaction. In one of these cases the subject stopped LCM because it was a 7-day study (there is no follow up for this case). In the other, the subject stopped LCM because of the transaminase/bilirubin elevation of 7x ULN. This case showed an immediate positive dechallenge. The case of hepatitis/ nephritis identified in the original review remains highly consistent with a delayed drug-induced multiorgan hypersensitivity reaction and should be mention in labeling. The fatal case of myocarditis and hepatitis is not inconsistent with a multiorgan hypersensitivity reaction. However, the informatior b(4)

Multiorgan hypersensitivity reactions are rare but potentially fatal. They have been reported with most anticonvulsants as well as with other drugs, such as sulfonamides, allopurinol, NSAIDs and dapsone. DRESS (another name used to describe these reactions) has been reported to occur in 1/10,000 subjects exposed to anticonvulsants. One case of consistent with DRESS (the case of hepatitis and nephritis) was reported among approximately 4,000 subjects exposed to LCM in this database. Two cases of rash and elevated transaminases, one of them with eosinophilia, were identified in a post-hoc analysis that is not routinely done with other anticonvulsants (or any drug). At this time it is unclear whether lacosamide is associated with a greater risk of multiorgan hypersensitivity than other anticonvulsants. Part of the problem is the lack of a validated definition and the inconsistency in coding and reporting of these events. Without an adequate comparative database it is impossible to draw definitive conclusions.

The potential for multiorgan hypersensitivity should be addressed in labeling under the WARNINGS and PRECAUTIONS section. Draft proposed labeling is presented in Appendix 7.

Although labeled, any adverse reaction consistent with multiorgan hypersensitivity/ DRESS/anticonvulsant hypersensitivity syndrome b(5)

A REMS/MedGuide may help reduce the risk of serious multiorgan hypersensitivity reactions further.

/ / / / / b(5)

Appendix 1. Reasons for exclusion from lacosamide epilepsy studies SP667, Sp754 and SP755.

	N	%
Subjects screened	1682	NA
Subjects randomized[a]	1311	NA
Subjects not randomized	371	NA
Inclusion Criteria		
Informed consent	0	0
Willing to comply	18	4.9
Age	1	0.3
Diagnosis of epilepsy	6	1.6
Refractory seizures and seizure frequency	111	29.9
Concomitant epilepsy treatment	13	3.5
Exclusion Criteria		
Previous LCM trial	0	0
Participation in other trial	0	0
History of drug abuse	4	1.1
Medical condition	18	4.9
Hypersensitivity[b]	0	0
Pregnancy and contraception	2	0.5
Liver tests[c]	35	9.4
Creatinine clearance[b]	3	0.8
Vital signs	8	2.2
ECG	27	7.3
Anaphylaxis or blood dyscrasias	1	0.3
Pseudo-seizures	2	0.5
Seizure clusters	3	0.8
Primary generalized seizures	3	0.8
Status epilepticus	2	0.5
Felbamate	2	0.5
Vigabatrin	7	1.9
Progressive CNS lesion or encephalopathy	0	0
Interference with ADME	2	0.5
Prohibited medications	38	10.2
Adverse event	15	4.0
Lack of efficacy	1	0.3
Unsatisfactory compliance	9	2.4
Subject withdrew consent	46	12.4
Lost to follow-up	10	2.7

ADME=absorption, distribution, metabolism, and excretion; CNS=central nervous system; ECG= electrocardiogram; LCM=lacosamide; NA=not applicable. a This includes 3 randomized and treated subjects from SP667 who were not included in the SP667 Safety Set or EP Pool S1 because of audit findings suggesting noncompliance with the protocol. b Applies to SP754 and SP755 only.
c For SP667, criterion also included serum creatinine. Note: Percentages are with respect to the number of subjects not randomized. Note: A subject may be counted under more than one reason for not being randomized. Source: Table in Pg. 2 of 6/13/08 response.

Appendix 2. Crude count of reports of Drug Rash with Eosinophilia and Systemic Symptoms associated with anticonvulsant drugs in AERS, through September 22, 2008. Source: WebVDME 6.0.

Trade name (Original from CBAERS)	N
Zonisamide	26
Carbamazepine	68
Phenytoin	30
Tegretol	36
Lamictal	25
Depakote	8
Phenobarbital Tab	5
Trileptal	5
Depakene	4
Valproic Acid	2
Phenytoin Sodium Cap	1
Phenytoin Sodium	1

As noted in this table, most anticonvulsants have at least one report of DRESS (except topiramate and leviteracetam).

None of the labels for these drugs use the term DRESS. Some labels mention multiorgan hypersensitivity reactions (Carbamazepine and Oxcarbamazepine, under PRECAUTIONS; Depakote under WARNINGS) but others do not (Zonisamide mentions potentially fatal reaction to sulfonamides under WARNINGS but not multiorgan hypersensitivity; Lamictal mentions hypersensitivity reactions and acute multiorgan failure, under WARNINGS, as if they were not related). Phenytoin?

Therefore, the language for multiorgan hypersensitivity with anticonvulsants (and with other drugs) is inconsistent throughout different labels. The FDA should work on making labeling consistent.

Appendix 3. Adverse events and laboratory value criteria suggestive of internal organ involvement (Group A) in subjects treated with lacosamide (8/14/08 submission)

MedDRA® SOC/Preferred term
Blood and lymphatic system disorders
Eosinophilia
Granulocytopenia
Leukopenia
Neutropenia
Pancytopenia
Thrombocytopenia
Lymphocytosis
Monocytosis
Mononucleosis syndrome
Blood disorder
Splenitis
Splenomegaly
Basophilia
White blood cell disorder

Cardiac disorders
Eosinophilic myocarditis[a]

Congenital, familial and genetic disorders
Congenital hepatomegaly

Gastrointestinal disorders
Colitis
Pancreatitis
Pancreatitis acute
Enterocolitis
Eosinophilic colitis[a]
Eosinophilic oesophagitis[a]
Hepatobiliary disorders
Hepatic Function Abnormal
Hepatotoxicity
Jaundice
Hepatitis
Hepatitis toxic
Hepatic failure
Hepatomegaly
Liver tenderness
Neonatal hepatomegaly
Hepatosplenomegaly[a]
Hepatosplenomegaly neonatal
Hepatic infiltration eosinophilic[a]

Immune system disorders
Hypersensitivity