CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22,253

Drug Name: Lacosamide

Indication(s):   Adjunctive Therapy for Partial Seizures

Applicant: Schwarz

Submission Date: Sept, 28 2007

Review Priority: Standard

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Keywords: log transformation, analysis of covariance, drop-outs, dose-response, multiple comparisons

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data from the three phase 3 trials seem to support the efficacy of Lacosamide as adjunctive therapy for partial seizures. The 400 mg/day dose was represented in each study and was statistically significantly better than placebo in each study. The 600 mg/day dose was also significantly better than placebo in the two studies it was included in, but there was no compelling evidence that the 600 mg/day dose provided added improvement over the 400 mg/day dose. The 200 mg/day dose was significantly better than placebo in one of the two studies in which it was included. Although in both studies in which it was included it's effect was numerically smaller than that of the 400 mg/day dose, in one, the difference was very small and, in both studies, the exploratory comparison of the difference between it and the 400 mg/day dose was not nominally significant.

1.2 Brief Overview of Clinical Studies

The primary trials included in this application, SP667 (US and Europe), SP754 (US only), and SP755 (non-US only), were designed to be adequate and well-controlled trials to evaluate the efficacy and safety of LCM 200mg/day (SP667 and SP755 only), 400mg/day, and 600mg/day (SP667 and SP754 only) versus placebo in subjects with uncontrolled partial-onset seizures taking 1, 2, or 3 (SP754 and SP755 only) antiepileptic drugs (AEDs) with or without vagal nerve stimulation (VNS). These 3 trials were similar in design; all were multicenter, randomized, double-blind, placebo-controlled trials to assess the efficacy and safety of 200 (SP667 and SP755 only), 400 (SP667, SP754, and SP755), and 600mg/day (SP667 and SP754 only) of LCM as adjunctive therapy in adult subjects with partial-onset seizures. In SP667, subjects were randomized in a 1:1:1:1 ratio to placebo, LCM 200mg/day, LCM 400mg/day, or LCM 600mg/day; in SP755, subjects were randomized in a 1:1:1 ratio to placebo, LCM 200mg/day, or LCM 400mg/day; and in SP754, subjects were randomized in a 1:2:1 ratio to placebo, LCM 400mg/day, or LCM 600mg/day.

The design of these studies represents a standard placebo-controlled, parallel group, adjunctive therapy trial in this indication similar to that used in the development of other newer AEDs. An 8-week Baseline Phase was considered necessary to adequately assess Baseline seizure frequency due to spontaneous fluctuations of seizure frequency in this patient population. A Baseline seizure frequency of at least 4 partial seizures per 28 days was deemed sufficiently high to detect both decreases and increases in seizure frequency during the Treatment Phase. Furthermore, the duration of the Maintenance Phase (12 weeks) was chosen to be consistent with the European Agency for the Evaluation of Medicinal Products (EMEA) "Note for the guidance on clinical investigation of medicinal products in the treatment of epileptic disorders" (EMEA, 2000).

1.3 Statistical Issues and Findings

Each of the three phase 3 studies had a protocol amendment to change the sample size. In the case of study 667 the reason for the change was that during the trial it was determined, based on tracking of patient completion status (blinded), that there were fewer dropouts than originally expected. Because of this the sponsor decided to reduce the number to be enrolled from 500 to 486 and the number to be randomized from 450 to 432. This change was made on 03 October 2003 after the first patient was enrolled (on 11 Feb 2002) and before the last subject completed (on 07 May 2004). For studies 754 and 755 the reason was that the original sample size calculations had been based on data from a different drug, Levetiracetam, since there was limited data on Lacosamide available at the time. Once study 667 was completed the sponsor wanted to update the sample size calculations for studies 754 and 755 using the Lacosamide data from study 667. For study 754 the sample size was increased from 60 to 100 subjects in the placebo group, 120 to 200 subjects in the 400mg/day group, and 60 to 100 subjects in the 600mg/day group. For study 755 the sample size was increased from 100 subjects per treatment group to 154 subjects per treatment group. The changes were made on 27 Jan 2005 for both study 754 and study 755, both of which were underway but not yet completed (754: 16 Aug 2006 and 755: 24 Jan 2006). However, the sponsor confirmed on April 11, 2008 that there was no unblinding of the internal trial data behind any of these sample size changes. Therefore, the sample size changes are not considered a serious issue.

The 600 mg/day Lacosamide group, the highest dose of Lacosamide studied for epilepsy and included in two of the three phase 3 trials, had a substantial number of dropouts: 42%, in study 667, as compared to 26% for the 400 mg/day group 21% for 200 mg/day and 11% for placebo and 33%, in study 754, as compared to 21% for the 400 mg/day group and 14% for the placebo group. The primary analysis of the double blind seizure rates was statistically significantly reduced for the 600 mg/day group as compared to the placebo group (p=0.0257 in study 667 and 0.0089 in study 754). The primary analysis was based on seizure data from the maintenance period only, if the patient had provided seizure data during the maintenance period and, where possible, when there was no data from the maintenance period, it was based on data from the titration period. The results for the 600 mg/day vs. placebo comparison were slightly sensitive to handling of dropouts as evidenced by the loss of significance when a patient's missing data after dropout was imputed with the patient's baseline seizure rate (p=0.1055 in study 667 and 0.0588 in study 754). This may be due to the high dropout rate for the 600 mg/day group. However, several other approaches to missing data imputation including imputing with the seizure rate during titration instead of during baseline did not lead to a loss of significance. The 400 mg/day group which had slightly less of a problem with dropouts was more robust to imputations for missing data after dropout.

Based on the primary intent-to-treat analysis of patients that had post-baseline seizure data there was very little evidence that the 600 mg/day dose provided any additional benefit beyond the 400 mg/day dose in either of the two studies in which it was studied. In addition the dropout rate was higher for the 600 mg/day group. Median percent changes from baseline in seizure rate were 39.0 for 400 mg/day and 39.6 for 600 mg/day in study 667, and, in study 754, they were 37.3 for 400 mg/day and 37.8 for 600 mg/day. In study 667 the primary analysis, of the logarithm

transformed double blind seizure rate, actually suggested that the 400 mg/day group had a numerically greater improvement than the 600 mg/day group.

2 INTRODUCTION

2.1 Overview

Lacosamide (LCM; SPM 927; previously referred to as harkoseride, [R]-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. Lacosamide is being developed for the treatment of adults with partial-onset seizures and adults with diabetic neuropathic pain. The associated IND is 57939.

The primary efficacy evaluation for the use of LCM for adjunctive therapy in adults with partial-onset seizures is based on 3 trials: SP667 (conducted in the United States [US] and Europe), SP754 (conducted in the US), and SP755 (conducted in Europe and Australia).

These 3 trials were similar in design; all were multicenter, randomized, double-blind, placebo-controlled trials to assess the efficacy and safety of LCM 200 (SP667 and SP755 only), 400, and 600mg/day (SP667 and SP754 only) as adjunctive therapy in adult subjects with partial-onset seizures. In SP667, subjects were randomized in a 1:1:1:1 ratio to placebo, LCM 200mg/day, LCM 400mg/day, or LCM 600mg/day, and in SP755, subjects were randomized in a 1:1:1 ratio to placebo, LCM 200mg/day, or LCM 400mg/day. However, in SP754, subjects were randomized in a 1:2:1 ratio to placebo, LCM 400mg/day, or LCM 600mg/day.

Subjects were male or female, age 18 to 65 years in SP667 and 16 to 70 years in SP754 and SP755. Included subjects had uncontrolled epilepsy with simple partial-onset seizures and/or complex partial-onset seizures with or without secondary generalization.
In addition, subjects were on a stable dosage regimen of 1 to 2 (SP667) or 1 to 3 (SP754 and SP755) concomitant AEDs with or without additional concurrent VNS. The dosage of concomitant AEDs was kept constant for ≥4 weeks prior to entry into the Baseline Phase and throughout the trial.

In each trial, subjects were enrolled and entered into an 8-week Baseline Phase. Only subjects who reported ≥4 partial-onset seizures per 28 days on the average, with seizure-free period no longer than 21 days during the Baseline Phase, were to be randomized. After randomization, the subjects began double-blind treatment as follows: a 4- (SP755) or 6-week (SP667 and SP754) forced titration up to the respective randomized dose of LCM (200, 400, or 600mg/day) or placebo (a 1-step back-titration of LCM 100mg/day or placebo was allowed in the case of intolerable adverse events [AEs] at the end of the Titration Phase), a 12-week Maintenance Phase on the achieved randomized (or back-titrated) dose, and either a 2-week Transition Phase or a 2- (SP755) or 3-week (SP667 and SP754) Taper Phase.

In order to facilitate trial blinding, subjects randomized to LCM 200 and 400mg/day in SP667 received placebo for the first 4 and 2 weeks of the double blind phase, respectively, and, similarly, subjects randomized to LCM 200mg/day in SP755 received placebo for the first 2 weeks.

2.2 Data Sources

The data for studies 667, 754, and 755 are located in the following directories, respectively.

\\cdsesub1\EVSPROD\NDA022253\0000\m5\datasets\ep-sp667\analyses
\\cdsesub1\EVSPROD\NDA022253\0000\m5\datasets\ep-sp754\analyses
\\cdsesub1\EVSPROD\NDA022253\0000\m5\datasets\ep-sp755\analyses

The study reports for studies 667, 754, and 755 are located in the following directories, respectively.

\\cdsesub1\EVSPROD\NDA022253\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\epilepsy\5351-stud-rep-contr\ep-sp667

\\cdsesub1\EVSPROD\NDA022253\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\epilepsy\5351-stud-rep-contr\ep-sp754

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3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 667

The first patient was enrolled on 11 Feb 2002 and the last subject completed on 07 May 2004.

3.1.1.1 Objectives

The primary objective of this trial was to evaluate the efficacy of SPM 927 (Lacosamide) administered concomitantly with 1 or 2 AEDs in subjects with or without additional vagal nerve stimulation (VNS) who currently have uncontrolled partial seizures with or without secondary generalization. The secondary objectives were to evaluate the safety of SPM 927 and the dose response relationship of SPM 927 with regards to efficacy and safety and to examine steady-state plasma concentrations of SPM 927 and concomitant AEDs during oral administration.

3.1.1.2 Study design

This trial was a multicenter, double-blind, placebo-controlled, 4-arm, trial of oral SPM 927 as adjunctive therapy in subjects with partial seizures with or without secondary generalization. The subjects were enrolled and entered into an 8-week pretreatment phase to obtain baseline data

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(Baseline Phase). After randomization the subjects were treated for up to 21 weeks in a double blind fashion: 6 weeks forced titration up to the respective randomized dose of SPM 927 (200mg/day, 400mg/day, or 600mg/day) or placebo (one step in back-titration of 100mg/day or placebo was allowed at the end of the Titration Phase), a 12-week Maintenance Phase on the achieved randomized dose, and either a 2-week Transition Phase or a 3-week Taper Phase. The 2-week Transition Phase was required for subjects who completed the Maintenance Phase and chose to enroll in an open-label extension trial of SPM 927 (study SP615), the primary objective of which is to collect long-term safety data for SPM 927. The 3-week Taper Phase was required for subjects who chose not to enroll in the open-label extension trial of SPM 927 or who did not complete the Maintenance Phase. The randomization ratio was 1 : 1 : 1 : 1 (Placebo : 200 mg/day : 400 mg/day : 600 mg/day). Randomization was stratified by country, and allocated to sites within each country.

Trial medication was to be administered in two equal oral doses per day at 12-hour intervals (4 tablets in the morning and 4 tablets in the evening). Subjects randomized to 600 mg/day were to titrate up by 100 mg/day per week for 6 weeks to 600 mg/day. Subjects randomized to 400 mg/day were to receive placebo during week 1 and week 2 and were to titrate up by 100 mg/day per week during week 3 through week 6 to 400 mg/day. Subjects randomized to 200 mg/day were to receive placebo during week 1 through week 4 and were to titrate up by 100 mg/day per week during week 5 and week 6 to 200 mg/day.

Diagnosis of partial seizures was to be based on the International Classification of Epileptic Seizures of the International League Against Epilepsy.

Each subject (or caregiver) kept a diary to note the daily seizure activity and seizure type from the beginning of the Baseline Period until the last visit. The following information was to be recorded in each subject's diary:

• Seizure type

• Seizure frequency

• Any AE's, including physical injury that occurred and any concomitant treatment that was used, if applicable.
The efficacy parameters were to be measured based on:

• Seizure records

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Table 1 shows the schedule of trial procedures.

Table 1 Study 667: Schedule of Trial Procedures

Procedures	Baseline Phase (8 weeks)			Treatment Phase (18 weeks)												
				Titration Phase (6 weeks)						Maintenance Phase (12 weeks)						
Visit [1]	V1	V2	V3	V4	V5	V6	V7	V8	V9 [5]	T1 [6]	V10	T2 [6]	V11	T3 [6]	V12 [7]	Unscheduled Visit [8]
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															
Call IVRS	X		X						X		X		X		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	X	X	X	X			X		X		X	X
Vital Signs (incl. BP/HR)	X	X	X [9]	X	X	X	X	X	X		X		X		X	X
Body Weight	X	X	X	X	X	X	X	X	X		X		X		X	X
Neurological Exam (complete)	X								X						X	
Neurological Exam (brief)			X	X	X	X	X	X			X		X			X
ECG (12-lead) [2]	X		X	X	X	X	X	X	X		X		X		X	
Laboratory Tests:																
Clinical Chemistry/Hematology	X		X	X	X	X	X	X	X		X		X		X	X
Urinalysis	X		X			X			X		X		X		X	X
Pregnancy Test	X [5]		X [U,10]			X [U]			X [U]		X [U]		X [U]		X [5]	
Concomitant AED Plasma Levels [3]	X		X	X	X	X	X	X	X		X		X		X	X
SPM 927 Plasma Level [3]			X	X	X	X	X	X	X		X		X		X	X
Clinical Global Impression Change									X						X	
Quality of Life in Epilepsy [4]			X						X						X	
Randomization			X													
Dispense Trial Medication			X	X	X	X	X	X	X		X		X		X	
Trial Medication Return				X	X	X	X	X	X		X		X		X	X [11]
Dispense Subject Diary	X	X	X	X	X	X	X	X	X		X		X		X	
Subject Diary Return		X	X	X	X	X	X	X	X		X		X		X	X [11]
Adverse Event Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BP, blood pressure; HR, heart rate; IVRS, interactive voice response system; S, serum; T, telephone contact; U, urine; V, Visit.

Copied from page 69 of study protocol

3.1.1.3 Statistical Analysis Plan

The Date of the first draft of the SAP was 14 Nov 2003. The final draft date was 11 Mar 2004 and the date of the final SAP was 17Jun 2004.

The assessment of efficacy is based on seizure frequency. There are two important efficacy variables. For the FDA, reduction in seizure frequency (variable 1) was to be the primary efficacy variable and the responder rate (variable 2) was to be the secondary efficacy variable. For Europe, the responder rate (variable 2) was to be the primary efficacy variable and the reduction in seizure frequency (variable 1) was to be the secondary efficacy variable.

For FDA:

1) Reduction in seizure frequency per 4 weeks from baseline to maintenance phase.

Seizure frequency per 4 weeks was to be calculated for the Baseline and post-Baseline Maintenance Phases as follows. For seizure frequency per 4 weeks, the number of days used to standardize the seizure frequency (SF) was to be based on the number of days (D) for which seizure information was provided: SF = (Number of Seizures) x (28 / D)

The inferential statistical analysis, based on an ANCOVA model with terms for treatment and region, was to be performed on log-transformed seizure frequency using the transformation of ln(x+1), where x is equal to the seizure frequency. Log-transformed average seizure frequency during the Baseline Phase was to be used as the covariate. The seizure frequency between treatment and placebo was to be compared using least squares (LS) means. The percent reduction over placebo was to be estimated as (1 - the exponentiated difference of LS means between treatment and placebo) multiplied by 100.

If a seizure cluster was reported, it was to be assigned to the correct seizure type. The highest recorded daily number of seizures of that seizure type during that phase for the corresponding subject was to be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures were recorded for that seizure type during the Treatment Phase, the value was to be set to number of seizures associated with the report of the cluster seizure.

There were to be approximately 80 sites from 9 countries in this trial, and it was planned to pool sites by region for analysis purposes. Sites were to be grouped into Eastern Europe (Hungary, Lithuania, Poland), Western Europe (France, Germany, Sweden, Switzerland, United Kingdom), Northeastern U.S., Southeastern U.S., and Western U.S.

The pair-wise comparison of the SPM 927 dose group versus placebo for reduction in seizure frequency described above was to be performed following a pre-defined hierarchical sequential rejective testing procedure. All null hypotheses were to be defined as no difference between the SPM 927 dose group and placebo and were to be tested using a two-sided test at the 5% level of significance. The hierarchical testing procedure was to start with the highest SPM 927 dose versus placebo. If the test was not statistically significant, the procedure was to stop, and no groups were to be declared different from placebo. If the test was statistically significant, the dose group was to be considered different from placebo and the procedure was to continue with the next highest dose. The procedure was to be repeated until the first time a test was not statistically significant. This testing procedure is considered a closed testing procedure and no adjustment of the significance level was to be necessary. Any comparisons between SPM 927 dose groups were to be considered exploratory and tested at the 5% significance level without multiplicity adjustment. In addition, a corresponding two-sided 95% confidence interval for the treatment effect was to be calculated for each pair-wise comparison.

2) Response to treatment was to be based on the percent change in seizure frequency. Subjects with at least a 50% reduction in seizure frequency were to be categorized as a responder. The responder rate between each treatment and placebo was to be analyzed using logistic regression with treatment and region as factors.

Other Secondary Efficacy Variables
• Reduction in seizure frequency per 4 weeks from baseline to treatment phase, defined as titration and maintenance phase.

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• Response to treatment of at least 50% from baseline to treatment phase, defined as titration and maintenance phase.
• Response to treatment of at least 75% from baseline to maintenance phase.
• Response to treatment of at least 75% from baseline to treatment phase, defined as titration and maintenance phase.
• Change in seizure frequency from baseline to maintenance phase differentiated by seizure type (i.e. simple partial seizures, complex partial seizures, partial seizures with secondary generalization).
• Change in seizure frequency from baseline to treatment phase, defined as titration and maintenance phase, differentiated by seizure type (i.e. simple partial seizures, complex partial seizures, partial seizures with secondary generalization).
• Achievement of "Seizure Free" Status (Yes/No).
"Seizure free" with respect to this trial means that no seizure, of the type counted in this trial, occurs during the maintenance phase.
(Status of subjects who discontinued the trial before reaching 28 days of maintenance phase was to be assumed not to be seizure free.)
• Proportion of seizure free days during maintenance phase.
• Clinical Global Impression of Change at the end of titration and maintenance phases.
• Changes in the assessment of Quality of Life in Epilepsy from baseline to the end of titration and maintenance phases [only for the subpopulation of subjects from United Kingdom (UK) and United States of America (USA)].

Statistical Analysis of Secondary Variables
Selected important secondary efficacy variables were to be analyzed using methods similar to the ANCOVA and logistic regression methods described previously. For the remaining efficacy variables and all safety variables, descriptive statistics by treatment group were to be presented.

Definition of Analysis Sets
The primary analysis set for the analysis of efficacy data was to be the Full Analysis Set (FAS), which was to include all subjects who were randomized, received at least one dose of trial medication, and had at least one post-baseline efficacy assessment. The Per Protocol Set (PPS) was to be defined during blind review, and include the subset of subjects from the FAS who had seizure frequency data in the maintenance phase and did not have major protocol violations.

Analysis of variables using the FAS or PPS was to be presented in an "as intended" manner (according to the intent-to-treat-principle) assigning subjects to their randomized target dose. Analysis of the primary efficacy variables, along with selected secondary efficacy variables, were to also be presented using the FAS in an "as treated" manner, assigning subjects to the SPM 927 dose actually received after titration.

Handling of Protocol Violators, Drop-outs and Missing Values
For subjects who discontinue prior to the maintenance phase, efficacy data were to be carried forward from the titration phase for inclusion in the maintenance phase analyses. Subjects who discontinued prior to any efficacy data collection were to not be included in the analysis (i.e., data were to not be carried forward from baseline). The seizure rate for subjects who

.completed a fraction of the treatment phase was to be calculated using the period of time that they were on trial medication.

Determination of Sample Size

A review of results from the SPM 927 pilot study FRC-01-201 that included 13 subjects, and from other clinical trials using different investigational drugs, indicated that an effect size index of about 0.4 for the primary variable could be assumed in the worst case. The effect size was calculated using a placebo-subtracted difference of −0.21 and a standard deviation of 0.45 on the log-transformed data. The difference of −0.21 on the log-transformed data is equivalent to approximately 19% reduction over placebo after exponentiation. Therefore, a sample of 100 subjects in each treatment is necessary to see a significant difference in change of seizure frequency between SPM 927 and placebo with a power of 90% and a significance level of 5%. Assuming a responder rate of 12% and 32% for placebo and SPM 927, respectively, a two-sided test at a significance level of 5% would provide approximately 90% power with 100 subjects per treatment arm. Sample size was estimated using nQuery v.3 for means and proportions.

Assuming 11% of subjects would discontinue prior to the start of the titration phase and up to 7% would be excluded from the Full Analysis Set, enrollment of approximately 486 subjects and randomization of approximately 432 subjects would provide 400 evaluable subjects for the primary analysis.

Change to the Originally Planned Sample Size

In Protocol Amendment 3 (28 Oct 2003) the number of subjects to be enrolled was re-estimated because trial dropout rates were lower than originally expected. The number of subjects needed for the primary analysis remained unchanged (N=400 total [100 per treatment arm]). Originally, it was assumed that 10% of subjects would discontinue prior to the start of the titration phase and up to 10 % would be excluded from the Full Analysis Set and, thus, enrollment of approximately 500 subjects and randomization of approximately 450 subjects would provide 400 evaluable subjects for the primary analysis.

Reviewer's Comment: In a response dated April 11, 2008 the sponsor stated that there was no unblinding of data for this re-estimation. This re-estimation of the number of patients was based on a trial management report that tracked the status of patients during the trial. The report revealed that the drop-out rate was lower than anticipated.

3.1.1.4 Patient Disposition

A total of 542 subjects were screened for this trial. A total of 497 subjects were enrolled in the trial and comprised the enrolled set (ES); 45 were screen failures. Of the 497 enrolled subjects, 421 were randomized and received at least one dose of trial medication and, hence, were eligible to be included in the safety set (SS). Because of audit findings suggesting noncompliance with the protocol, all 3 randomized and treated subjects at Site 12 were removed from the SS. As a result, 418 subjects were included in the SS. A total of 415 subjects also had at least one post-baseline efficacy assessment and are considered part of the FAS.

As noted above, the 3 subjects from Site 12 were excluded from all analyses presented in this report. However, both primary efficacy analyses and AE analysis were performed including the 3 subjects from Site 12 (data not shown), and no differences in data interpretation or conclusions were observed.

A total of 347 (83%) subjects completed the Titration Phase, 321 (77%) subjects completed the Maintenance Phase, and 312 (75%) subjects completed the entire trial. Of the subjects that discontinued participation in the trial prematurely, the most common reason for discontinuation was adverse events (5 subjects in the placebo group, 16 subjects in the 200mg/day group, 20 subjects in the 400mg/day group, and 32 subjects in the 600mg/day group).

Members of the trial team were unblinded to the treatment assignments of 2 subjects during the trial. The treatment assignment for Subject 12803 was unblinded after the subject committed suicide; this subject was randomized to receive 200mg/day SPM 927. The treatment assignment for Subject 18903 was unblinded after this subject took a double-dose of trial medication for 2 weeks; however, the subject had been taking placebo. The subject was withdrawn, however, due to this major protocol violation.

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Table 2 summarizes patient disposition in the trial

Table 2 Study 667 Patient Disposition

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
Note: This table was copied from pg 40 of the study report ep-sp667-report-body-2.pdf

3.1.1.5 Baseline Demographics

Subject demographics were comparable across treatment groups. The mean age was 40. Fifty four percent (54%) of patients were female and 92% were white. Vagus nerve stimulation (VNS) magnet therapy was used by 60 (14%) subjects. Of the 415 subjects in the FAS, 66 (16%) subjects took only 1 AED, and 349 (84%) subjects were regularly taking 2 concomitant AEDs. The most common concomitant AEDs were carbamazepine (31% of subjects), levetiracetam(30% of subjects), and lamotrigine (28% of subjects).

Table 3 summarizes Baseline Demographic and Disease Characteristics.

Table 3 Study 667 Baseline Demographic and Disease Characteristics

VARIABLE	SUBGROUP AND/ OR STATISTIC	PLACEBO	200 MG	400 MG	600 MG	ALL	PVALUE
age	Mean (SD)	39.1 (11.3)	39.9 (11.7)	41.3 (11.6)	39.5 (10.6)	40.0 (11.3)	0.384
gender	F -N(%)	50 (51.0)	61 (57.0)	56 (51.4)	61 (57.0)	228 (54.2)	0.699
gender	M -N(%)	48 (49.0)	46 (43.0)	53 (48.6)	46 (43.0)	193 (45.8)	0.699
race	Asian - N(%)		2 (1.9)			2 (0.5)	0.574
race	Black - N(%)	6 (6.1)	4 (3.7)	6 (5.5)	3 (2.8)	19 (4.5)	0.574
race	Caucasian -N(%)	89 (90.8)	98 (91.6)	100 (91.7)	101 (94.4)	388 (92.2)	0.574
race	Other - N(%)	3 (3.1)	3 (2.8)	3 (2.8)	3 (2.8)	12 (2.9)	0.574
Bmi (kg/m2)	Mean (SD)	27.4 (6.6)	26.3 (5.4)	27.3 (6.7)	26.5 (5.6)	26.8 (6.1)	0.317
height (m)	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	0.163
Weight (kg)	Mean (SD)	79.7 (20.8)	74.5 (17.2)	78.1 (19.4)	76.1 (19.6)	77.0 (19.3)	0.120
Baseline seiz frq per month	Mean (SD)	28.8 (50.0)	44.9 (143.8)	25.9 (36.4)	29.7 (71.9)	32.4 (86.6)	0.636
Baseline seiz frq per month	Median	11.1	13.0	13.0	11.0	12.0	
Baseline seiz frq per month	Min;Max	(3.8; 366.0)	(2.5; 1303.4)	(2.9; 227.6)	(3.2; 567.9)	(2.5; 1303.4)	

3.1.1.6 Sponsor's Results

Seizure frequency at baseline and at maintenance endpoint (defined as last observation carried forward: Maintenance Period if available, otherwise Titration Period) for the FAS is summarized in the following table. For subjects in the FAS, the median baseline seizure frequency for placebo and SPM 927 200, 400, and 600mg/day was 11, 13, 13, and 11 seizures per 4 weeks, respectively. The median seizure frequency at maintenance endpoint for these treatment groups was 10, 10, 7, and 8 seizures per 4 weeks, respectively.

Table 4 Study 667: Median Seizure frequency from Baseline to Maintenance Phase (FAS)

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*	-1	-3	-3	-4

*Change from Baseline represents median of individual subject changes from Baseline.
Copied from page 48 of study report

The inferential statistical analysis, based on ANCOVA with terms for treatment and region, was performed on log-transformed seizure frequency. Log-transformed average seizure frequency during the Baseline Phase was used as the covariate. 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. The results of statistical analysis for reduction of seizure frequency at maintenance endpoint are presented in the table below:

Table 5 Study 667: Statistical Analysis for Percent Reduction of Seizure Frequency over Placebo at Maintenance Endpoint Population: Full Analysis Set

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)

** Significant at the 0.0100 level
CI=confidence interval
Copied from page 49 of study report

The number of subjects with ≥50% response to treatment from Baseline to the Maintenance Phase is summarized for the FAS in the table below.

Table 6 Study 667: Statistical Analysis for ≥50% Responder at Maintenance Endpoint
Population: Full Analysis Set

Treatment	50% Responder	Unadjusted difference compared with placebo	Odds ratio	P-value for odds ratio
Placebo	22%	NA	NA	NA
600mg/day	38%	16.2%	2.2	0.0141*
400mg/day	41%	19.2%	2.5	0.0038**
200mg/day	33%	10.8%	1.7	0.0899

**Significant at the 0.01 level; *Significant at the 0.05 level
NA=not applicable
Copied from page 53 of sponsor's report

Statistically significant differences in responder rate were observed in the
SPM 927 400 and 600mg/day treatment groups compared with placebo.

Percent change in seizure frequency from Baseline to maintenance endpoint is depicted for the
FAS in the figure below:

Figure 1 Study 667: Median Percent Reduction of Seizure Frequency from Baseline to Maintenance Endpoint
Population: Full Analysis Set
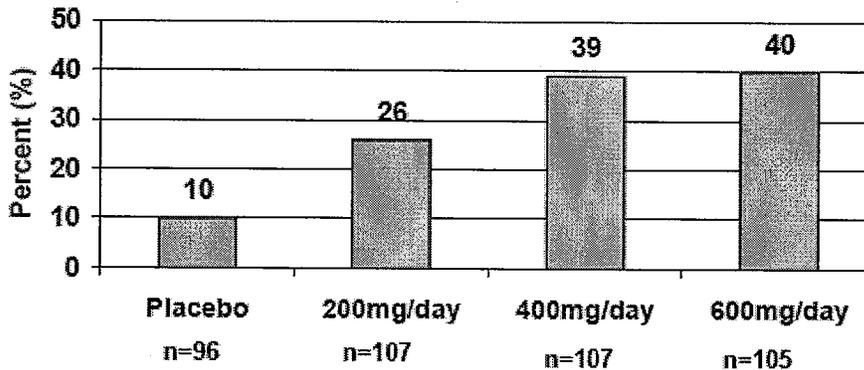
Sponsor's Subgroup Analyses
Subgroup analyses were performed by gender, use of vagus nerve stimulation, region, number of
concomitant antiepileptic drugs, lifetime antiepileptic drugs, use of selected concomitant
antiepileptic drugs, baseline simple partial seizures, baseline complex partial seizures, and
normalized dose by body weight. Treatment by subgroup interactions were observed for gender
and region. Thus, these analyses are described below.

Sponsor's Analysis of Gender Effects

Statistical analysis of treatment by gender interaction was performed on the continuous variable,
seizure frequency per month, revealing a significant treatment by gender interaction (p=0.0422).

To permit futher examination of this result, subjects with a 50% response to treatment at maintenance endpoint in the FAS is summarized by gender in the following table:.

Table 7 Study 667: Response to Treatment from Baseline to Maintenance By Gender (Full Analysis Set)

	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 (%)
Male				
n	46	46	53	45
At least 50% reduction	7 (15)	17 (37)	19 (36)	18 (40)
Female				
n	50	61	54	60
At least 50% reduction	14 (28)	18 (30)	25 (46)	22 (37)

Using both the continuous and categorical variables, SPM 927 reduced seizure frequency in both males and females. The statistically significant treatment by gender effect may be related to a higher placebo effect in females compared to males.

Sponsor's Analysis of Regional Effects
Statistical analysis of treatment by region interaction was performed on the continuous variable revealing a significant treatment by region interaction (p=0.0440). To examine this further, subjects with a 50% response to treatment at maintenance endpoint in the FAS is summarized by region in the following table.

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Table 8 Study 667: Responders to Treatment from Baseline to Maintenance By Region (Full Analysis Set)

	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 (%)
Northeast USA				
n	18	20	18	20
At least 50% reduction	2 (11)	5 (25)	9 (50)	6 (30)
Southeast USA				
n	16	16	19	15
At least 50% reduction	1 (6)	6 (38)	10 (53)	6 (40)
Western USA				
n	20	24	23	22
At least 50% reduction	7 (35)	13 (54)	7 (30)	8 (36)
Western Europe				
n	21	24	24	25
At least 50% reduction	6 (29)	5 (21)	8 (33)	11 (44)
Eastern Europe				
n	21	23	23	23
At least 50% reduction	5 (24)	6 (26)	10 (43)	9 (39)

copied from page 70 of 667 study report

Using both the continuous and categorical variables, SPM 927 reduced seizure frequency in each region. The statistically significant treatment by region effect may be related to a higher placebo effect in some regions compared to others as well as a variable effect of the 200mg/day dose across regions.

Reviewer's Comment: Note that when the 3 U.S. regions were combined there was no longer evidence of an interaction between region and treatment (p=0.84). Furthermore, there was no significant difference between the treatment effect in the pool of U.S. sites as compared to the pool of non-U.S sites (p=0.71).

Figure 2 Study 667: Variation of Treatment Group LSMeans by Region

```
LSMean Log(DBSeizRt)

    3.0

    2.8                              0

             2                       0
             0
    2.6
                 2                          0        4
                 0
    2.4     6       6        2        2             0
                                                      6
                                 6        4
    2.2     4                                6
                   4
                                                    2
    2.0
                            4

    1.8

         Eastern Euro   Northeast US   Southeast US   Western Euro   Western US

            N=90          N=76           N=66            N=94          N=89

                              Region
          Symbol: 0=Placebo   2=200   4=400   6=600
```
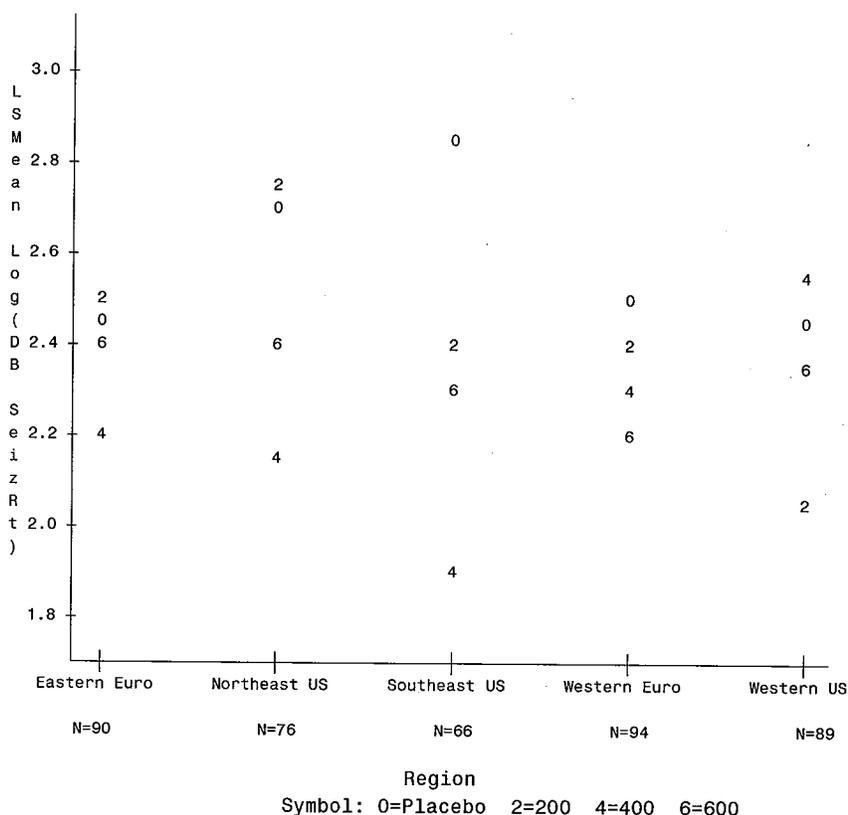
Sponsor's Efficacy Summary

The SPM 927 400 and 600mg/day treatment groups were statistically superior to the placebo group in seizure frequency reduction at maintenance endpoint (400mg/day p-value = 0.0023; 600mg/day p-value=0.0084). The percent reduction in seizure frequency over placebo was 28.4% (95% CI: 11.3, 42.2) and 21.3% (95% CI: 6.0, 34.1) for SPM 927 400mg/day and 600mg/day, respectively. The percent reduction in partial seizure frequency over placebo was 14.6% (p-value = 0.1010) for SPM 927 200mg/day indicating a numerically greater but not statistically significant difference. Similar positive findings were observed in the statistical analysis of responders, which is defined as subjects with at least 50% of seizure reduction at maintenance endpoint. The 50% responder rates for placebo, 400mg/day, and 600mg/day were 22%, 41% and 38%, respectively. The p-values for SPM 927 400 and 600mg/day when compared with placebo from logistic regression analysis were 0.0038 and 0.0141, which indicates the two SPM 927 dose groups are more likely than placebo group to have 50% responders. The 50% responder rate was 33% (p-value = 0.0899) for SPM 927 200mg/day, indicating a numerically greater but not statistically significant difference.

Seven subjects (all on SPM 927) were seizure-free throughout the 12-week Maintenance Phase. Results were similar across multiple efficacy assessments. Differing responses regarding gender and region were noted and may relate to differences in the placebo response. In addition, differences in responses by region may relate to a variable effect of the 200mg/day dose. Improvement was noted during the Titration Phase for both the 400 and 600mg/day SPM 927 treatment groups as early as 1 week after starting the active treatment. Clinically relevant improvement was consistent in these treatment groups during the Maintenance Phase. The reductions in seizure frequency observed in the 400 and 600mg/day SPM 927 groups were quantitatively similar.

Data from this trial in the sponsor's opinion clearly demonstrate that SPM 927 400 and 600mg/day treatment is an effective adjunctive treatment for partial seizures in patients with epilepsy. Trends observed in the primary analyses as well as statistically significant results in the Per Protocol analyses suggest that a dose of 200mg/day may be a minimally effective dose, i.e., a significant response to treatment was observed at this dose in some, but not all, analyses.

3.1.1.7 Reviewer's Results

The primary analysis was an analysis of covariance of the natural logarithm transformed double blind seizure rates during the maintenance period. The log transformed baseline rate was the covariate in the model and effects for pooled sites and each treatment group were also included in the model. This reviewer confirmed the sponsor's primary analysis which showed that the 400 and 600 mg/day doses had statistically significantly lower double blind seizure frequencies than placebo. The hierarchical conditional testing approach starting with the 600 mg dose was used to adjust for multiplicity. Testing stopped when the 200 mg vs. placebo dose was found to not be significant at the 0.05 level. Patients that had some post-baseline seizure data but none in the maintenance period had their endpoint based on their titration period data. Table 9 summarizes the results.

Table 9 Study 667: Reviewer's Results for Primary Analysis of Seizure Frequency over Maintenance Period

N	GROUP	MEDIAN BASELINE RATE	MEDIAN PERCENT CHANGE FROM BASE	MEAN OF LOG BASELINE RATES	LS MEAN OF LOG DB RATE	PCT REDUCTION OF DB RATE OVER PLACEBO*	95%CI	P-VALUE#
96	Placebo	11.3	10.7	2.76	2.58			
107	200 mg/day	13.0	25.6	2.86	2.42	-14.77	(-32.79; 3.24)	0.1390
107	400 mg/day	13.0	39.0	2.79	2.25	-27.85	(-43.09; -12.61)	0.0026
105	600 mg/day	11.0	39.6	2.73	2.33	-21.52	(-38.17; -4.87)	0.0257

*Percent Reduction over placebo equals the expression
100*(Exp{LS Mean of LCM LOG DB Rate - LS Mean of Plac LOG DB Rate} -1)
#P value based on ANCOVA of Log DB Rate adjusting for Log BS Rate, Pooled sites and Treatments

The significance of the comparisons with placebo were unaffected if instead of excluding days with missing seizure counts from the analysis we assumed that there were no seizures on such days. About 34 (8%) total subjects had diaries with some missing seizure counts during their double blind treatment periods (and 12 during baseline). As a worst case type of analysis for this issue we can assume that missing entries before dropout indicate 0 seizures for placebo at these times but we can still treat the missing seizure count as missing for the drug groups (thus these times are excluded from the denominator of the seizure rate). After doing this we find that the median percent change for placebo increases to 11.3 and the p-values for the comparisons with placebo of the log transformed seizure rate based on ANCOVA are 0.1669, 0.0035, and 0.0322 for the 200, 400, and 600 groups, respectively. Thus, the conclusions are not altered under this worst case type of analysis for missing diary entries before dropout.

Note that the primary analysis excluded all seizure counts during titration except when no post-titration data was available and that the 200 and 400 mg groups received placebo for the first 4 and 2 weeks of the titration period, respectively. If we include both titration and maintenance period seizures in the analysis then the median percent changes from baseline are 10.3, 17.7, 30.6, and 38.4 for the placebo, 200, 400, and 600 mg groups, respectively. The corresponding p-values for the comparisons with the placebo group based on the ANCOVA of the log transformed double blind period seizure rates are 0.1921, 0.0139, and 0.0073 for the 200, 400, and 600 mg groups, respectively. These results may be more conservative since they do not exclude seizures during titration and, yet, they support the primary analysis results for the 400 and 600 mg groups.

There was only limited evidence of dose response between the Lacosamide groups. The 400 and 600 mg/day groups had almost the same effects on the double blind seizure rate. The 200 mg/day effect was numerically smaller but there was not a statistically significant difference between it and the other LCM groups (exploratory comparisons: 200 vs. 400, p=0.113; 200 vs. 600, p=0.434). An exploratory test for a linear trend in the double blind seizure rates as a function of the Lacosamide dose (excluding the placebo group) suggested a lack of a significant linear trend (p=0.437).

3.1.1.7.1 Assessment of the Impact of Dropouts and Missing Data

Dropouts were most frequent for the 600 mg/day dose group (91% of Placebo, 82% of 200 mg/day, 77% of 400 mg/day, and 58% of 600 mg/day completed the maintenance phase of the double-blind treatment period). The results for the 400 mg/day vs. placebo comparison seemed relatively robust to various imputations of the seizure frequency for dropouts, which were done as sensitivity analyses (see Table 10). The 400 mg vs. placebo comparison was still significant for the subgroup of completers, as well as for the full analysis set augmented with several imputation methods for the imputation of seizure frequency between dropout and scheduled end of maintenance: imputation using observed frequency during titration phase, frequency during baseline period, or seizure frequency over last two weeks before dropout. For the sensitivity

analyses involving imputation of missing data after imputing the missing data the seizure frequency for the maintenance period was obtained by averaging observed pre-dropout and imputed post-dropout seizure frequencies. These were weighted according to the amount of time seizure data was collected prior to dropout and the remaining scheduled time post-dropout, respectively. The significance of the comparison of placebo to the 600 mg/day group which had more of a dropout problem was more sensitive to assumptions about seizure frequency for the dropouts. In particular, if the baseline seizure frequency rate was assumed for the time between dropout and the scheduled end of maintenance then the 600 mg/day vs. placebo comparison was not significant at the 0.05 level. This was also true if the imputation was instead done by using the seizure frequency from the last week before dropout.

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Table 10 Study 667: Assessment of the Impact of Dropouts on Primary Analysis

SUBGROUP OR IMPUTATION	N	GROUP	MEDIAN BASE SZRATE	MEDIAN PCTCHG FROM BASE	MEAN LOG (BASE SZRATE)	LSMEAN LOG(D.B. SZRATE)	PCTREDUCN OVER PLACEBO*	95% CI	P-VALUE#
COMPLETERS	86	PLACEBO	11.0	6.5	2.70	2.51			
	85	200 mg/day	13.0	24.7	2.81	2.31	-18.12	(- 35.59; -0.65)	0.0673
	80	400 mg/day	13.0	36.2	2.79	2.10	-33.93	(- 48.23; - 19.63)	0.0002
	61	600 mg/day	11.5	40.4	2.80	2.15	-30.27	(- 46.55; - 13.99)	0.0027
Impute Missing with Rate over Last 2 Weeks	96	Placebo	11.3	3.2	2.76	2.58			
	107	200 mg/day	13.0	18.0	2.86	2.42	-15.14	(- 33.26; 2.97)	0.1324
	107	400 mg/day	13.0	30.9	2.79	2.23	-29.50	(- 44.54; - 14.47)	0.0014
	105	600 mg/day	11.0	33.3	2.73	2.33	-22.04	(- 38.75; -5.34)	0.0233
Impute Missing with Baseline Rate	96	Placebo	11.3	2.7	2.76	2.57			
	107	200 mg/day	13.0	13.2	2.86	2.42	-14.01	(- 29.53; 1.50)	0.1016
	107	400 mg/day	13.0	22.7	2.79	2.27	-25.53	(- 38.96; - 12.11)	0.0015
	105	600 mg/day	11.0	1.0	2.73	2.42	-13.92	(- 29.50; 1.67)	0.1055

3.1.1.8 Secondary Analyses

This reviewer also verified the analysis of responders who were defined as patients with at least a 50% change from baseline. This was based on data from the maintenance period only for patients that had maintenance period seizure data and it was based on titration period data for patients that did not have any maintenance period seizure data.

The percentages of responders were 21% for the placebo group, 33% for the 200 mg/day group, 40% for the 400 mg/day group, and 37% for the 600 mg/day group. The 400 mg/day and 600 mg/day group patients were statistically significantly more likely to be responders by this definition than placebo patients. In particular, the ratio of the odds of being a responder in the 400 mg/day group to the odds of being a responder on placebo was 2.48 (95% C.I.: 1.34, 4.59). For the 600 mg/day versus placebo comparison the odds ratio was 2.19 (95% C.I.: 1.18, 4.09). The odds ratio for the 200 mg/day group versus placebo was not statistically significantly different from 1. The estimate was 1.78 and the associated confidence interval was (.95, 3.34).

3.1.2 Study 754

The first subject was enrolled on 18 Mar 2004 and the last subject completed on 16 Aug 2006.

3.1.2.1 Study Design and Statistical Analysis Plan

Study SP754 was a multi-center, randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of 400 and 600mg/day of SPM 927 in subjects with partial seizures with or without secondary generalization. There were to be approximately 85 sites, all in the United States (USA). A total of approximately 500 subjects with partial seizures were to be enrolled into an 8-week Baseline Phase. At the end of the Baseline Phase, subjects were to be randomized in a double-blind fashion to 1 of 3 treatment arms (placebo, SPM 927 400mg/day, or SPM 927 600mg/day) in a 1:2:1 ratio. The maximum duration of a subject's trial participation was to be 29 weeks. The maximum duration of trial medication administration was to be 21 weeks. The Treatment Phase was comprised of the following: 6 weeks forced titration to the respective randomized dose of SPM 927 (400 or 600mg/day) starting with 100 mg/day at week 1 or placebo (a 1-step back-titration of 100mg/day or placebo is allowed at the end of the Titration Phase), 12 weeks maintenance on the achieved randomized dose, and either 2 weeks transition or 3 weeks taper. The 2-week Transition Phase (bringing subjects to a dose of 200mg/day SPM 927) was to be required for subjects who completed the Maintenance Phase and who chose to enroll in an open-label extension trial of SPM 927. The 3-week Taper Phase was to be required for subjects who completed the study but chose not to enroll in the open-label extension trial of SPM 927 or who did not complete the Maintenance Phase.

The study design was very similar to study 667 except that there was no 200 mg/day group in this study and the randomization was 1:2:1 (placebo: LCM 400 mg/day: LCM 600 mg/day).

Determination of sample size

Effect size, standard deviation, and responder rate estimates described below are based on efficacy results obtained from LCM Trial SP667.

Assuming an effect size of 0.434, in which the effect size was calculated using a placebo-subtracted difference of -0.334 and a common standard deviation of 0.77 on the log-transformed data, the difference of -0.334 on the log-transformed data is equivalent to approximately 28% reduction over placebo after exponentiation.[1] With this effect size, power of 94%, and a 2-sided test at the 5% level of significance, a sample of 100 subjects in placebo and 200 subjects in LCM 400mg/day groups would be needed.

Assuming an effect size of 0.375, in which the effect size was calculated using a placebo-subtracted difference of -0.240 and a common standard deviation of 0.64 on the log-transformed data, the difference of -0.240 on the log-transformed data is equivalent to approximately 21% reduction over placebo after exponentiation. With this effect size, power of 75%, and a 2-sided test at the 5% level of significance, a sample of 100 subjects in placebo and 100 subjects in LCM 600mg/day groups would be needed. With this sample, a power of 90% can be expected should a placebo subtracted difference of -0.295 be observed.

It was estimated that 500 enrolled subjects would yield 400 subjects valid for the primary analysis of efficacy. Screening was allowed to be continued until at least 400 subjects randomized to their corresponding treatment arm had provided at least 1 post-baseline seizure frequency observation.

Changes to the Plan through Protocol Amendments

Two protocol amendments were issued (27 Jan 2005 and 19 May 2006).
The following changes were made as a result of protocol amendment 1:

• The sample size needed to achieve adequate statistical power for both primary endpoints was increased from 60 subjects in the placebo group, 120 subjects in the 400mg/day group, and 60 subjects in the 600mg/day group to 100 subjects in the placebo group, 200 subjects in the 400mg/day group, and 100 subjects in the 600mg/day group. This change was based on an analysis of efficacy data from the LCM trial SP667, where a larger standard deviation, as well as a larger placebo response for the primary efficacy endpoint, was observed compared to the assumptions used in the original protocol. The assumptions for effect size and standard deviation in the original protocol (ie, an effect size of 0.522 with a standard deviation of 0.45 for the 400mg/day group [US primary endpoint]; 12% and 35% responder rates for placebo and 400mg/day SPM 927, respectively [EU primary endpoint]) were drawn from a levetiracetam trial. In the amendment it was assumed that the effect size and standard deviation from trial SP667 would provide more realistic assumptions for the calculation of the sample size needed to achieve 90% statistical power in this trial. Given the 1:2:1 ratio of subjects randomized to placebo, 400mg/day, and 600mg/day, it was estimated that 500 enrolled subjects would yield 400 subjects valid for the primary analysis of efficacy.

---

[1] The percent reduction over placebo = $(1 - exp [LSM_{TRT} - LSM_{PBO}]) \times 100\%$

Reviewer's Comment: In a response dated April 11, 2008 the sponsor stated that there was no unblinding of the internal trial data for this sample size change. Instead, it was felt that the data from the recently completed trial, study 667, would provide a better estimate of the Lacosamide treatment effect than the original estimate which was based on a trial for a different drug, Levetiracetam.

The statistical hierarchical testing procedure was changed to start with the LCM 400mg/day dose group versus the placebo group (the original protocol stated in error that the testing procedure was to begin with the LCM 600mg/day dose group versus the placebo group).

Analysis Plan (Date of Final Draft SAP: 06 Jan 2006 Date of Final SAP: 13 Oct 2006)

Seizure frequency per 28 days was to be calculated for the Baseline and post-Baseline Maintenance as described previously for study 667. The inferential statistical analysis, based on an ANCOVA model with terms for treatment and pooled site, was to be performed on log-transformed seizure frequency using the transformation of $\ln(x+1)$, where x is equal to the seizure frequency. Log-transformed average seizure frequency during the Baseline Phase was to be used as the covariate.

The analysis plan is very similar to that from study 667 except for the following issues:
The hierarchical testing procedure was to start with the SPM 927 400mg/day dose group versus the placebo group instead of starting with the 600 mg/day group.

Assumptions for the parametric model described above were to be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus baseline covariate values and treatment. An assessment was to be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations were to be identified prior to unblinding, and an assessment was to be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If it was deemed that a non-parametric method was warranted, an ANCOVA model on rank of percent change in seizure frequency per 28 days with terms for treatment and pooled site was to be employed as the primary analysis. Ranked seizure frequency per 28 days during the Baseline Phase was to be used as a covariate.

There were to be approximately 85 sites from the USA in this trial, and it was planned to pool sites by enrollment size for analysis purposes. Those sites randomizing a small (1, 2, or 3) number of subjects were to be pooled together. Those sites randomizing a small-to-medium (4 or 5) number of subjects were to be pooled together. Those sites randomizing a medium (6 or 7) number of subjects were to be pooled together. Those sites randomizing a medium-to-large (8 or 9) number of subjects were to be pooled together. Those sites randomizing a large (10, 11, 12, 13, or 14) number of subjects were to be pooled together. And those sites randomizing the largest (≥15) number of subjects were to be pooled together. Each pooled site was to contain at least 20 randomized subjects and the largest pooled site was to be no more than three times larger than the smallest pooled site.

3.1.2.2 Patient Disposition

A total of 556 subjects were screened for this trial. A total of 489 subjects were enrolled in the trial and comprised the Enrolled Set (ES); 54 subjects were screen failures and 13 additional subjects were excluded from the enrolled count due to not meeting all screening criteria although classified as Baseline Failures based on the trial termination CRF. Of the 489 enrolled subjects, 405 were randomized. All the 405 randomized subjects received at least 1 dose of trial medication and comprise the safety set (SS). A total of 402 subjects also had at least 1 post-Baseline efficacy assessment and are considered part of the Full Analysis Set (FAS). Table 11 summarizes patient disposition.

Table 11 Study 754: Patient Disposition (Safety Set)

	Placebo N=104 n (%)	LCM 400mg/day N=204 n (%)	LCM 600mg/day N=97 n (%)	Total N=405 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.

Note: This table was copied from pg 56 of the sponsor's study report

3.1.2.3 Baseline Demographics and Disease Characteristics

Baseline demographics and disease characteristics are shown in Table 12. The mean age overall was 38.3 years. A total of 397 subjects were <65 years old and 8 subjects were ≥65 years old. Overall, 205 (50.6%) subjects were female and 200 (49.4%) subjects were male. The majority of subjects were White (81.5% of all subjects).

One notable difference in baseline demographics was that the placebo group weighed significantly less on average than the 400 mg group as well as the combined drug groups.

Although there were some numerical differences in the group baseline seizure rates in terms of the mean and median, none of the drug group differences from placebo were statistically significant at the nominal level.

Table 12 Study 754 Baseline Demographics and Disease Characteristics

VARIABLE	SUBGROUP AND/OR STATISTIC	PLACEBO (N=104)	LCM 400 MG/DAY (N=204)	LCM 600 MG/DAY (N=97)	ALL	PVALUE
age	Mean (SD)	38.1 (12.0)	39.1 (12.4)	36.8 (11.8)	38.3 (12.1)	0.894
Age Group	<65-N(%)	104 (100.0)	197 (96.6)	96 (99.0)	397 (98.0)	0.092
Age Group	≥65-N(%)		7 (3.4)	1 (1.0)	8 (2.0)	0.092
race	asian-N(%)	1 (1.0)	3 (1.5)	1 (1.0)	5 (1.2)	0.979
race	black-N(%)	12 (11.5)	18 (8.8)	8 (8.2)	38 (9.4)	0.979
race	caucasian-N(%)	84 (80.8)	166 (81.4)	80 (82.5)	330 (81.5)	0.979
race	other-N(%)	7 (6.7)	17 (8.3)	8 (8.2)	32 (7.9)	0.979
sex	female-N(%)	55 (52.9)	100 (49.0)	50 (51.5)	205 (50.6)	0.796
sex	Male-N(%)	49 (47.1)	104 (51.0)	47 (48.5)	200 (49.4)	0.796
bmi	Mean (SD)	26.4 (5.5)	29.3 (7.5)	28.2 (7.1)	28.3 (7.0)	0.004
Diagnosis Epil Time (YR)	Mean (SD)	25.4 (13.3)	24.5 (13.2)	23.4 (13.3)	24.5 (13.2)	0.346
Weigh(kg)	Mean (SD)	75.4 (18.5)	83.9 (21.6)	80.8 (21.3)	81.0 (21.0)	0.004
Baseline Seizfrq/mo	Mean (SD)	46.9 (109.5)	43.1 (124.2)	27.9 (35.1)	40.4 (105.6)	0.351
Baseline Seizfrq/mo	Median	15.0	11.5	16.5	13.5	
Baseline Seizfrq/mo	Min;Max	(3.5; 840.5)	(3.5; 1253.0)	(3.5; 256.7)	(3.5; 1253.0)	

Overall, the mean time since diagnosis was 24.5 years and subjects participating in this trial had epilepsy that was difficult to control. Fewer than 50% of subjects in any single group had a disease history including simple partial seizures, whereas between 80% and 90% of subjects had a disease history including complex partial seizures.

Vagus nerve stimulation magnetic therapy was used by 119 (29.6%) subjects overall. Among the 402 subjects in the FAS, a majority of all subjects (55%) regularly took 2 concomitant AEDs, while approximately 27% of all subjects took 3 concomitant AEDs, and approximately 18% of all subjects took 1 concomitant AED. A total of 66 (16.4%) subjects had taken 1-3 AEDs in their lifetime, 136 (33.8%) subjects had taken 4-6 AEDs in their lifetime, and 194 (48.3%) subjects had taken 7 or more AEDs in their lifetime.

Overall in the SS, the most common concomitant AEDs were levetiracetam, lamotrigine, carbamazepine, and oxcarbazepine which were taken by 160 (39.5%), 146 (36.0%), 102 (25.2%), and 86 (21.2%) of all subjects, respectively. As allowed per protocol, Lorazepam was typically used as rescue medication. Overall, it was taken by 17 (4.2) patients (3 (2.9) placebo, 9 (4.4) 400 mg, and 5 (5.2) 600 mg).

3.1.2.4 Sponsor's Results

The table below displays for the FAS the median seizure frequency per 28 days for the Baseline and Maintenance Phases for each treatment group. For subjects in the FAS, the median Baseline seizure frequency per 28 days for placebo, LCM 400mg/day, and LCM 600 mg/day was 15.0, 11.5, and 16.5, respectively. The median seizure frequency per 28 days for the Maintenance Phase for these treatment groups was 11.8, 6.9, and 9.7, respectively.

Table 13 Study 754: Median seizure frequency per 28 days by treatment (Full Analysis Set)

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.
Copied from page 71 of study report

The results of statistical analyses for the change in seizure frequency at the end of Maintenance Phase are presented in the table below. Statistically significant reductions in seizure frequency were observed in the LCM 400mg/day and 600mg/day treatment groups compared to placebo.

Table 14 Study 754: Statistical analysis for percent reduction of seizure frequency over placebo for the Maintenance Phase (Full Analysis Set)

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
Copied from page 72 of study report

Statistical analysis of subjects with ≥50% reduction in seizure frequency (50% responder rate) from Baseline to the Maintenance Phase is summarized for the FAS in the table below. Statistically significant differences in 50% responder rates were observed in the LCM 400mg/day and 600mg/day treatment groups compared to placebo.

Table 15 Study 754: Statistical analysis of ≥50% reduction in seizure frequency for Maintenance Phase (FAS)

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
Copied from page 75 of study report

3.1.2.5 Reviewer's Results

The primary analysis was an analysis of covariance of the natural logarithm transformed double blind seizure rates during the maintenance period. The log transformed baseline rate was the covariate in the model and effects for pooled sites and each treatment group were also included in the model. This reviewer confirmed the sponsor's primary analysis which showed that the 400 and 600 mg/day doses had statistically significantly lower double blind seizure frequencies than placebo. The hierarchical conditional testing approach starting with the 400 mg dose was used to adjust for multiplicity. Patients that had some post-baseline seizure data but none in the maintenance period had their endpoint based on their titration period data.

This reviewer's results for the primary analysis are summarized in Table 16.

Table 16 Study 754: Primary Analysis Result

GROUP	N	GROUP	MEDIAN BASELINE RATE	MEDIAN PERCENT CHANGE FROM BASE	MEAN OF LOG BASELINE RATES	LS MEAN OF LOG DB RATE	PCT REDUCTION OF DB RATE OVER PLACEBO*	95%CI	P-VALUE#
Placebo	104	Placebo	15.0	20.8	3.02	2.62			
LCM 400	201	LCM 400mg/day	11.5	37.3	2.84	2.38	-21.15	(- 35.49; -6.81)	0.0108
LCM 600	97	LCM 600mg/day	16.5	37.8	2.94	2.33	-24.76	(- 40.72; -8.79)	0.0089

```
*Percent Reduction over placebo equals the expression
100*(Exp{LS Mean of LCM LOG DB Rate - LS Mean of Plac LOG DB Rate} -1)
#P value based on ANCOVA of Log DB Rate adjusting for Log BS Rate, Pooled sites and Treatments
```

The significance of the comparisons with placebo were unaffected if instead of excluding days with missing seizure counts from the analysis we assumed that there were no seizures on such days. About 56 (14%) total subjects had diaries with some missing seizure counts during their double blind treatment periods (and 23 during baseline). As a worst case type of analysis for this issue we can assume that missing entries before dropout indicate 0 seizures for placebo at these times but we can still treat the missing seizure count as missing for the drug groups (thus these times are excluded from the denominator of the seizure rate). After doing this we find that the median percent change for placebo increases to 21.6 and the p-values for the comparisons with placebo of the log transformed seizure rate based on ANCOVA are 0.0138 and 0.0110 for the 400 and 600 groups, respectively. Thus, the conclusions are not altered under this worst case type of analysis for missing diary entries before dropout.

Note that the primary analysis excluded all seizure counts during titration except when no post-titration data was available and that the 400 mg group received placebo for the first 2 weeks of the titration period. If we include both titration and maintenance period seizures in the analysis then the median percent changes from baseline are 21.0, 33.8, and 32.7 for the placebo, 400, and 600 mg groups, respectively. The corresponding p- values for the comparisons with the placebo group based on the ANCOVA of the log transformed double blind period seizure rates are 0.0058 and 0.0127 for the 400 and 600 mg groups, respectively. These results may be more conservative since they do not exclude seizures during titration and yet they support the primary analysis results.

Although it was not part of the formal testing, this reviewer examined the comparison between the 400 and 600 mg/day Lacosamide dose groups. There was very little difference between the 400 mg/day and 600 mg/day groups (p=0.623). The study was not powered for this comparison but the existing evidence suggests that there may not be any additional benefit of the 600 mg/day dose over the 400 mg/day dose.

3.1.2.5.1 Assessment of the Impact of Dropouts and Missing Data

Dropouts were most frequent for the 600 mg/day dose group (87% of Placebo, 79% of 400 mg/day, and 67% of 600 mg/day completed the maintenance phase of the double-blind treatment period). The results for the 400 mg/day vs. placebo comparison seemed relatively robust to various imputations of the seizure frequency which were done as sensitivity analyses for dropouts. The 400 mg vs. placebo comparison was still significant for the subgroup of completers, as well as for the full analysis set augmented with several imputation methods for the imputation of seizure frequency between dropout and scheduled end of maintenance: imputation using observed frequency during titration phase, frequency during baseline period, or seizure frequency over last two weeks before dropout. For the sensitivity analyses involving imputation of missing data after imputing the missing data the seizure frequency for the maintenance period was obtained by averaging observed pre-dropout and imputed post-dropout seizure frequencies. These were weighted according to the amount of time seizure data was collected prior to dropout and the remaining scheduled time post-dropout, respectively. The significance of the comparison of placebo to the 600 mg/day group which had more of a dropout problem was more sensitive to assumptions about seizure frequency for the dropouts. In particular, if the baseline seizure frequency rate was assumed for the time between dropout and the scheduled end of maintenance then the 600 mg/day vs. placebo comparison was not significant at the 0.05 level, although the nominal p-value was still less than 0.06.

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Table 17 Study 754: Sensitivity Analyses for the Assessment of the Impact of Missing Data/Dropouts

Subgroup OR Imputation	N	GROUP	MEDIAN BASE SzRate	MEDIAN PCTCHG From Base	Mean LOG (BASE SzRATE)	LSMEAN LOG(D.B. SzRate)	PCTREDUCN Over Placebo*	95% CI	P-VALUE#
Completers	90	Placebo	14.0	16.2	2.98	2.57			
	161	LCM 400mg/day	11.0	30.2	2.83	2.27	-25.74	(-40.27; -11.22)	0.0031
	65	LCM 600mg/day	15.5	40.4	2.88	2.15	-33.93	(-49.90; -17.95)	0.0009
Impute Missing After Dropout with Rate during last 2 weeks	103	Placebo	15.0	14.5	3.02	2.62			
	200	LCM 400mg/day	11.5	27.4	2.83	2.36	-22.68	(-36.86; -8.50)	0.0063
	95	LCM 600mg/day	16.5	30.6	2.94	2.30	-27.35	(-42.95; -11.75)	0.0037
Impute Missing After Dropout with Baseline Rate	104	Placebo	15.0	10.5	3.02	2.63			
	201	LCM 400mg/day	11.5	15.6	2.84	2.43	-18.15	(-31.24; -5.05)	0.0146
	97	LCM 600mg/day	16.5	12.9	2.94	2.45	-16.51	(-32.09; -0.93)	0.0588

3.1.2.6 Secondary Analyses

This reviewer also verified the analysis of responders who were defined as patients with at least a 50% change from baseline. This was based on data from the maintenance period only for patients that had maintenance period seizure data and it was based on titration period data for patients that did not have any maintenance period seizure data.

The percentages of responders were 18% for the placebo group, 39% for the 400 mg/day group, and 41% for the 600 mg/day group. The 400 mg/day group patients were statistically significantly more likely to be responders by this definition than placebo patients. In particular, the ratio of the odds of being a responder in the 400 mg/day group to the odds of being a responder on placebo was 2.90 (95% C.I.: 1.64, 5.15). The odds ratio for the 600 mg/day group versus placebo was also statistically significantly different from 1. The estimate was 3.13 and the associated confidence interval was (1.65, 5.95).

3.1.3 Study 755

The first subject was enrolled on 07 Jun 2004 and the last subject completed on 24 Jan 2006.

3.1.3.1 Objectives

The primary objective of this trial is to evaluate the efficacy of SPM 927 administered concomitantly with 1, 2, or 3 AEDs in subjects with or without additional VNS who currently have uncontrolled partial seizures with or without secondary generalization.
The secondary objectives are to evaluate the safety of SPM 927, the dose-response relationship of SPM 927 with regards to efficacy and safety, and to examine steady-state plasma concentrations of SPM 927 and concomitant AEDs during oral administration of SPM 927.

3.1.3.2 Study Design

This Phase 3, double-blind, placebo-controlled, parallel-group trial was to be conducted at approximately 80 sites in Europe and Australia. A screening visit is conducted to evaluate subject suitability for enrollment. This visit can be conducted on more than 1 day, although it should not be done over longer than a week. A total of approximately 577 subjects with partial seizures were to be enrolled into an 8-week Baseline Phase. At the end of the Baseline Phase, subjects were to be randomized (1:1:1) in a double-blind fashion to 1 of 3 treatment arms: placebo or SPM 927 (200 or 400mg/day). The duration of the trial was to be 26 weeks including an 8-week Baseline Phase and an 18-week Treatment Phase. The Treatment Phase was to be comprised of the following: 4 weeks forced titration up to the respective randomized dose of SPM 927 or placebo (a 1-step back-titration of 100mg/day or placebo is allowed at the end of the Titration Phase), 12 weeks maintenance on the achieved randomized dose, and 2 weeks transition or taper. Trial medication was to be orally administered twice daily (at ~12-hour intervals, once in the morning and once in the evening). During the 4-week Titration Phase, dose titration was to begin at 100mg SPM 927 or placebo. The 200 mg group was to be on placebo for the first two weeks of the titration phase. SPM 927 was to be titrated in 100mg/week steps to 200 or 400mg/day.

During the 12-week Maintenance Phase, subjects were to be maintained on the dose achieved during the Titration Phase based on the randomized dose. Subjects who required dose reduction during the Maintenance Phase were to be withdrawn from the trial.

3.1.3.3 Statistical Analysis Plan

There were to be 76 sites from 12 countries in Europe (United Kingdom, France, Spain, Sweden, Finland, Germany, Hungary, Lithuania, Poland, Russia, Croatia, and Czech Republic) and Australia in this trial, and it was planned to pool sites and countries by geographic region for analysis purposes. Countries enrolling a small number of subjects were to be pooled such that each pooled site contained at least 20 randomized subjects and the largest pooled site was no more than three times larger than the smallest pooled site. Utilizing this strategy, the United Kingdom and Australia were to be combined to form a pooled site, Finland and Sweden were to be combined to form a pooled site, and France and Spain were to be combined to form a pooled site. The remaining countries mentioned above (ie, Germany, Hungary, Lithuania, Poland, Russia, Croatia, and Czech Republic) were to each stand alone as an individual pooled site.

For subjects who discontinued prior to the Maintenance Phase, efficacy data was to be carried forward, utilizing the LOCF principle, from the Titration Phase for inclusion in the Maintenance Phase analyses, unless otherwise noted.

Seizure frequency per 28 days was to be calculated for the Baseline and post-Baseline Maintenance Phases as described for study 667. The inferential statistical analysis, based on an ANCOVA model with terms for treatment and pooled site, was to be performed on log-transformed seizure frequency using the transformation of $\ln(x+1)$, where x is equal to the seizure frequency. Log transformed average seizure frequency during the Baseline Phase was to be used as the covariate. The seizure frequency between treatment and placebo was to be compared using least squares (LS) means. The percent reduction over placebo was to be estimated as (1 - the exponentiated difference of LS means between treatment and placebo) multiplied by 100. If a seizure cluster was reported, it was to be assigned to the correct seizure type and the highest recorded daily number of seizures of that seizure type during that phase for the corresponding subject was to be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures were recorded for that seizure type during that phase, the value was to be set to number of seizures associated with the report of the cluster seizure.

Assumptions for the parametric model described above were to be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment was to be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is warranted, an ANCOVA model on rank of percent change in seizure frequency per 28 days with terms for treatment and pooled site was to be employed as the primary analysis. Ranked seizure frequency per 28 days during the Baseline Phase was to be used as a covariate.

The pair-wise comparison of LCM dose group versus placebo for reduction in seizure frequency described above was to be performed following a pre-defined hierarchical sequential rejective testing

procedure. All null hypotheses were to be defined as no difference between the LCM dose group and placebo and were to be tested using a two-sided test at the 5% level of significance. The hierarchical testing procedure was to start with the higher LCM dose (ie, 400mg/day) versus placebo. If the test was not statistically significant, the procedure was to stop, and no groups would be declared different from placebo. If the test was statistically significant, the 400mg/day group would be considered different from placebo and the procedure would continue with the 200mg/day dose group. If the test was not statistically significant for the 200mg/day group, the procedure would stop and only the 400mg/day group would be considered different from placebo. If the test for the 200mg/day group was statistically significant, both the 200 and 400mg/day groups would be considered different from placebo. This testing procedure is considered a closed testing procedure and no adjustment of the significance level was to be necessary. In addition, a corresponding two-sided 95% confidence interval for the treatment effect was to be calculated for each pair-wise comparison.

Efficacy Measures

The assessment of efficacy is based on partial seizure frequency. There are different primary efficacy variables for FDA and Europe. For the FDA, efficacy was to be determined by the change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase.

Secondary efficacy variables

- Efficacy was to be determined by the proportion of responders where a responder is a subject experiencing a 50% or greater reduction in partial seizure frequency from Baseline to the Maintenance Phase.

• Proportion of subjects experiencing a ≥25% to <50%, 50 to 75%, or >75% reduction in partial seizure frequency from Baseline to the Maintenance Phase

• Change in partial seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration + Maintenance)

• Proportion of subjects experiencing a ≥25% to <50%, 50 to 75%, or >75% reduction in partial seizure frequency from Baseline to the entire treatment (ie, Titration + Maintenance)

• Proportion of subjects experiencing no change in partial seizure frequency (between <25% reduction and <25% increase in partial seizure frequency from Baseline to the entire treatment (ie, Titration + Maintenance)

• Proportion of subjects experiencing an increase in partial seizure frequency (≥25% increase in partial seizure frequency from Baseline to the entire treatment (ie, Titration + Maintenance)

• Proportion of subjects experiencing rebound seizures defined as an increase in partial seizure frequency ≥100% from Baseline to the Taper Phase

• Change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase by seizure type

• Change in partial seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration + Maintenance) by seizure type

At the beginning of visit 2 (Baseline phase) the investigator should assess the partial seizure frequency over the 4-week period in the subject diary to ensure that the subject is eligible to continue in the trial. The subject must have reported at least 1 partial onset seizure, with seizure-free period no longer than 21 days and without any uncountable seizures due to clustering since the last visit. At the beginning of visit 3 (end of baseline) the investigator should assess the partial seizure frequency over the 8-week Baseline Phase in the subject diary. On the basis of the diary, the subject must have reported at least 4 partial onset seizures per 28 days on average, with no more than 21 consecutive seizure-free days, and without any uncountable seizures due to clustering during the 8-week Baseline Phase.

The efficacy parameters were to be measured based on:
• Seizure Records
• Clinical Global Impression of Change
• Patient's Global Impression of Change
• Seizure Severity Scale
• QOLIE-31

Each subject was to keep a diary provided by the sponsor to note the daily seizure activity from the beginning of the
Baseline Phase until the last visit, and was to record the following information:
• Seizure type
• Seizure frequency
• Any AEs, including physical injury that occurred and any concomitant treatment that was applied, if applicable.
Table 18 provides the schedule of trial procedures in study 755.

Table 18 Study 755: Schedule of Trial Procedures - All subjects

Procedures	Baseline Phase (8 weeks)			Treatment Phase (16 weeks) Titration Phase (4 weeks)				Maintenance Phase (12 weeks)						Unscheduled Visit [9]
Visit [1]	V1	V2	V3	T1	V4	T2	V5 [6]	T3	V6	T4	V7	T5	V8 / EW [4]	
Weeks in Trial	-8	-4	0	1	2	3	4	6	8	10	12	14	16	
Pregnancy Test	X [5]		X [11,4]				X [6]				X [7]		X [5]	
Con AED Plasma concentrations [3]	X		X				X	X					X	X
SPM 927 Plasma concentration [1]			X		X		X	X					X	X
QOLIE-31			X										X	
Clinical Global Impression Change													X	
Patient's Global Impression Change													X	
Seizure Severity Scale			X										X	
Call IVRS	X		X		X		X		X		X		X	
Randomization			X											
Dispense Trial Medication			X [5]		X		X		X		X	X		
Trial Medication Return					X		X		X		X	X		X [10]
Dispense Subject Diary	X	X	X		X		X		X		X		X	
Subject Diary Return		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
Assessment of epilepsy surgery/VNS	X												X	

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Clinical Global Impression of Change
The Clinical Global Impression of Change should be completed by an investigator or sub-investigator. It was to be used to assess the improvement or change in the subject's clinical status that resulted from SPM 927, including evaluation of seizure frequency and intensity, the occurrence of AEs, and the subject's overall functional status.

Definition of analysis sets
The primary analysis set for the efficacy data was to be the Full Analysis Set (FAS), and was to include all subjects who were randomized, received at least 1 dose of trial medication, and had at least 1 post-baseline seizure frequency data. The secondary analysis set for the efficacy data was to be the Per Protocol Set, which was to include all subjects in the FAS with at least 1 seizure frequency data from the Maintenance Phase and who did not have major protocol deviations. A third analysis set for the efficacy data, called the "Completers" Set (CS), was to include all subjects from the FAS who completed the Maintenance Phase. The Safety Set (SS) was to include all randomized subjects who took at least 1 dose of trial medication.

Statistical analysis of primary variable

Efficacy was to be determined by the change in seizure frequency per 28 days from baseline to the Maintenance Phase. Seizure frequency per 28 days was to be calculated as ([number of seizures over the specified time interval] divided by [number of days in the interval]) multiplied by 28. For subjects who prematurely discontinued the trial, last observation carried forward (LOCF) method was to be applied in the following manner to obtain a seizure frequency estimate for the Maintenance Phase:
Subjects discontinued prematurely during the Titration Phase: seizure frequency were to be calculated using all available data in the Titration Phase and carrying that forward for the Maintenance Phase. Subjects discontinued prematurely during the Maintenance Phase: seizure frequency was to be calculated using all available data in the Maintenance Phase and carrying that forward for the entire Maintenance Phase. Subjects completed the Maintenance Phase: seizure frequency was to be calculated using all data from the Maintenance Phase. If a seizure cluster is reported, the highest recorded daily seizure frequency during the Treatment Phase was to be used as the imputed seizure frequency for the day on which the cluster occurred.

The primary analysis was an analysis of covariance of the double blind seizure frequency with terms for treatment and center (properly pooled), on log-transformed seizure frequency using the transformation of $\ln(X+1)$, where X is the seizure frequency. Log-transformed baseline seizure frequency was to be used as a covariate. The seizure frequency between treatment and placebo was to be compared using least squares means (LSMs). The percent reduction over placebo was to be estimated as $100 \times [\ 1 - \exp(LSM_{TRT} - LSM_{PBO})\ ]$.

It was planned to properly pool centers by geographic region or country. The final strategy for pooling of centers was to be determined at the Blinded Data Review meeting. The pairwise

comparisons of SPM 927 dose groups versus placebo for analyzing the reduction in seizure frequency described above were to be performed following a predefined hierarchical sequential rejective testing procedure. All null hypotheses were to be defined as no difference between the SPM 927 dose group and placebo and were to be tested using a 2-sided test at the 5% level of significance. The hierarchical testing procedure was to start with the SPM 927 400mg/day dose group versus the placebo group. If the test was not statistically significant, the procedure was to stop and no groups were to be declared different from placebo. If the test was statistically significant, the dose group was to be considered different from placebo and the procedure was to continue with the SPM 927 200mg/day dose group. This testing procedure is considered a closed testing procedure and no adjustment of the significance level was to be necessary. The comparisons between SPM 927 dose groups were to be considered exploratory and tested at the 5% significance level. In addition, a corresponding 2-sided 95% confidence for the treatment effect was to be calculated for each pairwise comparison. If the normality assumption for the primary efficacy variable did not hold, a non-parametric analysis was also to be performed as described for study 754. The descriptive statistics for seizure frequency and its absolute and percentage reduction from baseline with and without using LOCF method were to be summarized for each post-baseline visit, Maintenance Phase and entire Treatment Phase (ie, Titration and Maintenance) by treatment group. The count and percentage for subject with a 50% or more reduction in seizure frequency with and without using LOCF method were to be presented for each post-baseline visit, Maintenance Phase and Treatment Phase (ie, Titration and Maintenance) by treatment group.

Handling of protocol violators, drop-outs and missing values
For subjects who discontinued prior to the Maintenance Phase, all available seizure frequency data were to be carried forward from the Titration Phase for the Maintenance Phase analysis. For subjects who prematurely discontinued during the Maintenance Phase, all available seizure frequency data in the Maintenance Phase were to be carried forward for the entire Maintenance Phase. Subjects who discontinued prior to any efficacy data collection were to not be included in the analysis (ie, data were to not be carried forward from Baseline).

Determination of Sample Size
Assuming an effect size of 0.371, in which the effect size was calculated using a placebo-subtracted difference of -0.286 and a common standard deviation of 0.77 on the log-transformed data, the difference of -0.286 on the log-transformed data is equivalent to approximately 25% reduction over placebo after exponentiation. With this effect size, power of 90%, and a 2-sided test at the 5% level of significance, a sample of 154 subjects in placebo and 154 subjects in SPM 927 400mg/day groups would be needed. Note that the Effect size, standard deviation, and responder rate estimates are based on efficacy results obtained from SPM 927 Trial SP667. The percent reduction over placebo equals $(1 - \exp [\text{LSMean}_{TRT} - \text{LSMean}_{PBO}]) \times 100\%$. It is estimated that 577 enrolled subjects would yield 462 subjects valid for the primary analysis of efficacy. Screening may be continued until at least 462 subjects randomized to their corresponding treatment arm have provided at least 1 post-baseline seizure frequency observation.

Protocol Amendments

The SP755 trial protocol (19 Dec 2003) was amended once (27 Jan 2005). The following was one of the key changes made as a result of protocol amendment 1:

• The sample size needed to achieve adequate statistical power for both primary endpoints was increased from 100 subjects per treatment group to 154 subjects per treatment group. This change was based on an analysis of efficacy data from the LCM trial SP667, where a larger standard deviation, as well as a larger placebo response for the primary efficacy endpoint, was observed compared to the assumptions used in the original protocol. The assumptions for effect size and standard deviation in the original protocol (ie, an effect size of 0.467 with a standard deviation of 0.45 [US primary endpoint]; 12% and 32% responder rates for placebo and SPM 927, respectively [EU primary endpoint]) were drawn from a levetiracetam trial. In the amendment this was changed because it was assumed that the effect size and standard deviation from trial SP667 would provide more realistic assumptions for the calculation of the sample size needed to achieve 90% and 80% statistical power in this trial for the US and EU endpoints, respectively. Given the 1:1:1 ratio of subjects randomized to placebo, 200mg/day, and 400mg/day, it was estimated that 577 enrolled subjects would yield 462 subjects valid for the primary analysis of efficacy.

Reviewer's Comment: In a response dated April 11, 2008 the sponsor stated that there was no unblinding of the internal trial data for this sample size change. Instead, it was felt that the data from the recently completed trial, study 667, would provide a better estimate of the Lacosamide treatment effect than the original estimate which was based on a trial for a different drug, Levetiracetam.

3.1.3.4 Patient Disposition

A total of 584 subjects were screened for this trial. A total of 546 subjects were enrolled in the trial and comprised the enrolled set (ES); 32 subjects were screen failures and 6 subjects denoted as Baseline failures did not meet all Screening criteria and were excluded from the count of enrolled subjects. Of the 546 enrolled subjects, 485 were randomized. All of the 485 randomized subjects received at least 1 dose of trial medication and comprise the safety set (SS). A total of 477 subjects also had at least 1 post-Baseline efficacy assessment and are considered part of the full analysis set (FAS).

In the SS, a total of 435 (89.7%) subjects completed the Titration Phase, 403 (83.1%) subjects completed the Maintenance Phase, and 399 (82.3%) subjects completed the entire trial. Of the subjects who discontinued the trial prematurely, the most common reason for discontinuation was adverse event (9 subjects in the placebo group, 10 subjects in the LCM 200mg/day group, and 25 subjects in the LCM 400mg/day group).

Table 19 summarizes patient disposition in the trial.

Table 19 Study 755 Disposition (Full Analysis Set)

	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.
Copied from page 74 of study report

3.1.3.5 Baseline Demographics

Table 20 summarizes baseline demographics and disease characteristics. The mean age overall was 37.8 years. A total of 479 subjects were <65 years old and 6 subjects were ≥65 years old. Overall, 250 (51.5%) subjects were male and 235 (48.5%) subjects were female. The majority of subjects were White (99.2% of all subjects). Six subjects that were ≥65 years old (Subjects 102311, 110103, 102314, 110503, 110505, and 124406) participated in this trial. With the exception of Subject 124406, all of these subjects were female. Three of these subjects completed the trial (and transitioned into the open-label extension trial) and 3 subjects

discontinued early from the trial. Among the 3 subjects that discontinued the trial early, 1 subject withdrew due to a nonserious AE (vertigo) during the Maintenance Phase, 1 subject withdrew consent during the Titration Phase (no AEs reported), and 1 subject withdrew due to a nonserious AE (diplopia) during the Titration Phase.

Table 20 Study 755: Baseline Demographics and Disease Characteristics

Demographic	Statistic and or Subgroup	Placebo	LCM 200 mg/day	LCM 400 mg/day	ALL	Pvalue
Age	Mean (SD)	38.5 (10.9)	36.9 (11.7)	37.9 (13.0)	37.8 (11.9)	0.326
Age Group < 65	< 65-N(%)	163 (100.0)	161 (98.8)	155 (97.5)	479 (98.8)	0.124
Age Group	≥ 65-N(%)		2 (1.2)	4 (2.5)	6 (1.2)	0.124
Race	asian-N(%)	1 (0.6)		2 (1.3)	3 (0.6)	0.401
race	black-N(%)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	0.401
race	caucasian-N(%)	162 (99.4)	162 (99.4)	157 (98.7)	481 (99.2)	0.401
sex	Female-N(%)	72 (44.2)	73 (44.8)	90 (56.6)	235 (48.5)	0.043
sex	Male-N(%)	91 (55.8)	90 (55.2)	69 (43.4)	250 (51.5)	0.043
bmi	Mean (SD)	25.9 (5.0)	25.2 (4.8)	25.3 (5.1)	25.4 (5.0)	0.196
epilepsy diagnosis (years)	Mean (SD)	21.1 (12.2)	22.9 (12.3)	22.8 (13.2)	22.3 (12.6)	0.165
Weigh(kg)	Mean (SD)	74.7 (17.1)	74.9 (16.9)	72.2 (16.9)	74.0 (17.0)	0.480
Baseline seiz frq per month	Mean (SD)	22.3 (31.5)	94.5 (645.7)	41.8 (202.8)	53.0 (392.7)	0.225
Baseline seiz frq per month	Median	10.0	11.4	10.2	10.5	
Baseline seiz frq per month	Min,Max	(3.6; 220.0)	(4.0; 8048.7)	(3.1; 2415.8)	(3.1; 8048.7)	

Overall, the mean time since diagnosis was 22.3 years and subjects participating in this trial had epilepsy that was difficult to control.

Overall in the Safety Set (SS), the most common AEDs taken prior to Baseline were carbamazepine, valproate, lamotrigine, and topiramate which were taken by 232 (47.8%), 159 (32.8%), 148 (30.5%), and 137 (28.2%) of subjects, respectively, and the frequency of use was similar across all treatment groups.

A total of 272 subjects (56.1%) recorded use of at least 1 concomitant medication. Note that subjects were expected to have been on a stable regimen of AEDs for the 4 weeks prior to Baseline, during Baseline, and throughout the treatment. Changes in AED treatment regimen were noted as major protocol deviations. Overall in the SS, the most common concomitant AEDs were carbamazepine, valproate, lamotrigine, and topiramate which were taken by 232 (47.8%), 159 (32.8%), 148 (30.5%), and 137 (28.2%) of all subjects, respectively.

Vagus nerve stimulation magnetic therapy was used by 37 subjects (7.8%) overall. Among the 477 subjects in the FAS, a substantial number of all subjects (approximately 50%) regularly took 2 concomitant AEDs, while approximately 37% of all subjects took 3 concomitant AEDs and approximately 13% of all subjects took 1 concomitant AED. A total of 142 subjects (29.8%) had taken 1-3 AEDs in their lifetime, 156 subjects (32.7%) had taken 4-6 AEDs in their lifetime, and 174 subjects (36.5%) had taken 7 or more AEDs in their lifetime.

3.1.3.6 Sponsor's Results

In the sponsor's opinion this double-blind, placebo-controlled Phase 3 trial supports that LCM at doses of 200mg/day and 400mg/day (100 and 200mg bid, respectively) is an effective treatment for partial seizures when added to 1 to 3 approved concomitant AEDs in subjects experiencing difficult to control partial seizures with or without secondary generalization.

The LCM 200mg/day and 400mg/day treatment groups were statistically superior to the placebo group in the reduction of seizure frequency per 28 days for the Maintenance Phase (200mg/day p-value=0.0223; 400mg/day p-value=0.0325). The percent reduction in seizure frequency over placebo was 14.4% (95% CI: 2.2, 25.1) and 15.0% (95% CI: 1.4, 26.8) for LCM 200mg/day and 400mg/day, respectively. Similar positive findings were observed in the statistical analysis of responders, which is defined as subjects with at least 50% seizure reduction for the Maintenance Phase. The 50% responder rates for placebo, 200mg/day, and 400mg/day were 25.8%, 35.0% and 40.5%, respectively. The p-value for LCM 400mg/day when compared with placebo was 0.0063, which indicates this LCM dose group is more likely than the placebo group to have 50% responders. Although not statistically significant, LCM 200mg/day showed a numerically improved treatment difference over placebo.

Eleven subjects were seizure-free throughout the 12-week Maintenance Phase; 8 (3.1%) subjects were taking LCM and 3 (2.1%) subjects were taking placebo. Results were similar across multiple efficacy assessments. In both the LCM 200mg/day and 400mg/day treatment groups, the reduction in seizure frequency was greater than placebo starting by the end of the second week of active treatment. Clinically relevant improvement was consistent over time in these treatment groups during the Maintenance Phase. Overall, in both the clinician rated and patient rated clinical global improvement, CGIC and PGIC, a greater percentage of subjects in the LCM 400mg/day treatment group were considered improved compared to placebo; however, this difference was not statistically significant. The percentage of subjects considered improved in the LCM 200mg/day treatment group was not different than the percentage of improved subjects in the placebo treatment group.

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Table 21 shows the median seizure frequency per 28 days for the full analysis set.

Table 21 Study 755: Median seizure frequency per 28 days by treatment Population: FAS

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.

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Table 22 provides the percent reduction over placebo as determined from the primary analysis of the log transformed seizure rates.

Table 22 Study 755: Statistical analysis for percent reduction of seizure frequency over placebo for the Maintenance Phase Population: Full Analysis Set

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

CI=confidence interval; LCM=lacosamide

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The median percent reduction in seizure frequency from Baseline to the Maintenance Phase appears to be similar between LCM 200mg/day and 400mg/day (see Figure 3).

Figure 3 Study 755: Median percent reduction of seizure frequency from Baseline to Maintenance Phase Population: Full Analysis Set
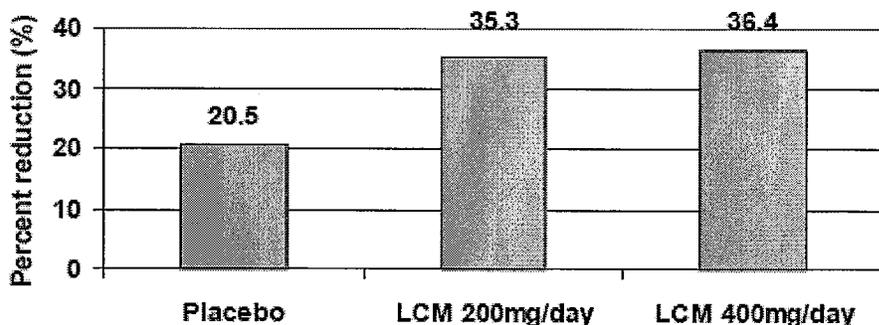
Statistical analysis of subjects with ≥50% reduction in seizure frequency (50% responder rate) from Baseline to the Maintenance Phase is summarized for the FAS in the table below.

Table 23 Study 755: Statistical analysis of 50% responder rates for the Maintenance Phase Population: Full Analysis Set

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

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Subgroup analyses

Subgroup analyses for the FAS were performed by gender, use of VNS, pooled site, number of concomitant AEDs, lifetime AEDs, use of selected concomitant AEDs, Baseline simple partial seizures, Baseline complex partial seizures, Baseline partial seizures with secondary generalization, and normalized dose by body weight. For the reduction in seizure frequency during the Maintenance Phase, statistical analysis of treatment by Baseline complex partial seizures or partial seizures with secondary generalization subgroup was performed revealing a statistically significant interaction (p-value=0.0427). This significant interaction may reflect the greater reductions in seizure frequency observed with LCM 200mg/day and LCM 400mg/day when compared to placebo for subjects identified in this subgroup.

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3.1.3.7 Reviewer's Results

The primary analysis was an analysis of covariance of the natural logarithm transformed double blind seizure rates during the maintenance period. The log transformed baseline rate was the covariate in the model and effects for pooled sites and each treatment group were also included in the model. This reviewer confirmed the sponsor's primary analysis which showed that the 200 and 400 mg/day doses had statistically significantly lower double blind seizure frequencies than placebo. The hierarchical conditional testing approach starting with the 400 mg dose was used to adjust for multiplicity. Patients that had some post-baseline seizure data but none in the maintenance period had their endpoint based on their titration period data. Table 24 summarizes this reviewer's results for the primary analysis.

Table 24 Study 755: Primary Analysis Result of Double Blind Seizure Frequency During Maintenance (FAS)

GROUP	N	GROUP	MEDIAN BASELINE RATE	MEDIAN PERCENT CHANGE FROM BASE	MEAN OF LOG BASELINE RATES	LS MEAN OF LOG DB RATE	PCT REDUCTION OF DB RATE OVER PLACEBO*	95%CI	P-VALUE#
Placebo	159	Placebo	9.9	20.5	2.65	2.42			
LCM 200	160	LCM 200mg/day	11.5	35.3	2.90	2.27	-13.62	(-26.13; -1.10)	0.0483
LCM 400	158	LCM 400mg/day	10.3	36.4	2.65	2.26	-15.06	(-27.33; -2.79)	0.0272

```
*Percent Reduction over placebo equals the expression
100*(Exp{LS Mean of LCM LOG DB Rate - LS Mean of Plac LOG DB Rate} -1)
#P value based on ANCOVA of Log DB Rate adjusting for Log BS Rate, Pooled sites and Treatments
```

The significance of the comparisons with placebo were unaffected if instead of excluding days with missing seizure counts from the analysis we assumed that there were no seizures on such days. About 43 (9%) total subjects had diaries with some missing seizure counts during their double blind treatment periods (and 33 during baseline). As a worst case type of analysis for this issue we can assume that missing entries before dropout indicate 0 seizures for placebo at these times but we can still treat the missing seizure count as missing for the drug groups (thus these times are excluded from the denominator of the seizure rate). After doing this we find that the median percent change for placebo remains 20.5 and the p-values for the comparisons with placebo of the log transformed seizure rate based on ANCOVA are 0.0572 and 0.0319 for the 200 and 400 groups, respectively. Thus, the conclusions for the 400 mg group are not altered under this worst case type of analysis for missing diary entries before dropout.

Note that the primary analysis excluded all seizure counts during titration except when no post-titration data was available and that the 200 mg group received placebo for the first 2 weeks of the titration period. If we include both titration and maintenance period seizures in the analysis then the median percent changes from baseline are 18.2, 29.6, and 33.2 for the placebo, 200, and 400 mg groups, respectively. The corresponding p- values for the comparisons with the placebo

group based on the ANCOVA of the log transformed double blind period seizure rates are 0.0664 and 0.0129 for the 200 and 400 mg groups, respectively. These results may be more conservative since they do not exclude seizures during titration.

An exploratory comparison of the 200 and 400 mg/day groups suggested a lack of a significant difference (p=0.819) between them. However, it should be noted that the study was not powered for this comparison.

3.1.3.7.1 Assessment of the Impact of Dropouts and Missing Data

Dropouts were slightly more frequent for the 400 mg/day dose group (87% of Placebo, 83% of 200 mg/day, and 77% of 400 mg/day completed the maintenance phase of the double-blind treatment period). The results for the 400 mg/day vs. placebo comparison seemed relatively robust to various imputations of the seizure frequency for dropouts which were done as sensitivity analyses. The 400 mg vs. placebo comparison was still significant for the subgroup of completers, as well as for the full analysis set augmented with several imputation methods for the imputation of seizure frequency between dropout and scheduled end of maintenance: imputation using observed frequency during titration phase, frequency during baseline period, or seizure frequency over last two weeks before dropout. The results for these sensitivity analyses are shown in Table 25.

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Table 25 Study 755: Sensitivity Analyses for the Assessment of Missing Data/Dropout Impact

Subgroup OR Imputation	N	GROUP	MEDIAN BASE SzRate	MEDIAN PCTCHG From Base	Mean LOG (BASE SzRATE)	LSMEAN LOG(D.B. SzRate)	PCTREDUCN Over Placebo*	95% CI	P-VALUE#
Completers	141	Placebo	9.9	17.4	2.64	2.36			
	136	LCM 200mg/day	11.5	27.7	2.86	2.19	-15.35	(-28.02; -2.68)	0.0297
	122	LCM 400mg/day	10.0	30.8	2.67	2.16	-17.90	(-30.50; -5.31)	0.0121
Impute Missing After Dropout with Rate during last 2 weeks	159	Placebo	9.9	14.0	2.65	2.43			
	157	LCM 200mg/day	11.5	26.7	2.92	2.26	-16.02	(-28.36; -3.69)	0.0202
	157	LCM 400mg/day	10.3	25.0	2.65	2.27	-14.88	(-27.29; -2.47)	0.0308
Impute Missing After Dropout with Baseline Rate	159	Placebo	9.9	9.6	2.65	2.42			
	160	LCM 200mg/day	11.5	21.3	2.90	2.30	-11.05	(-22.53; 0.43)	0.0761
	158	LCM 400mg/day	10.3	19.4	2.65	2.31	-10.37	(-21.90; 1.17)	0.0963

3.1.3.8 Secondary Analyses

This reviewer also verified the analysis of responders who were defined as patients with at least a 50% change from baseline. This was based on data from the maintenance period only for patients that had maintenance period seizure data and it was based on titration period data for patients that did not have any maintenance period seizure data.

The percentages of responders were 25% for the placebo group, 34% for the 200 mg/day group, and 40% for the 400 mg/day group. The 400 mg/day group patients were statistically significantly more likely to be responders by this definition than placebo patients. In particular, the ratio of the odds of being a responder in the 400 mg/day group to the odds of being a

responder on placebo was 2.03 (95% C.I.: 1.25, 3.30). The odds ratio for the 200 mg/day group versus placebo was not statistically significantly different from 1. The estimate was 1.57 and the associated confidence interval was (.97, 2.56).

3.2 Evaluation of Safety

Please see the medical officer's safety review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Note that the p-values displayed in section 4 are not adjusted for multiple testing and are just presented for exploratory purposes to give a sense of the magnitude of the corresponding effects.

4.1.1 Gender

About 51% of all patients were female and 49% were male. Overall, there was no compelling evidence that the treatment effect varied by gender (p=0.30). The sponsor reported an apparent difference in treatment effect by gender in study 667. However, in that study the treatment effect favored Lacosamide, at least for the 400 and 600 groups, in both genders. As can be seen in Figure 4 there was a larger placebo response and a lower response for 200 mg/day in the females than the males which might explain the significance of the interaction (p=0.04). The drug response was numerically larger for the 400 and 600 mg/groups in the females than the males which compensated for the higher placebo response in females. Furthermore, there was no compelling evidence that the treatment effect varied across gender for the two doses that were found to be effective in study 667 (p=0.889) when the low dose was excluded from the analysis.

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Figure 4 Study 667: Assessment of Consistency of Treatment Effects by Gender

```
          2.7 +
L                                                            0
S
M
e         2.6 +
a
n             2
              |
L         2.5 +
o             0
g
(
D         2.4 +                                              6
B
              |
S
e         2.3 +                                              4
i             6
z
R         2.2 +                                              2
t
)
              4
          2.1 +
              |
              +-----------------------------------+
            FEMALE                               MALE

                          Gender
```
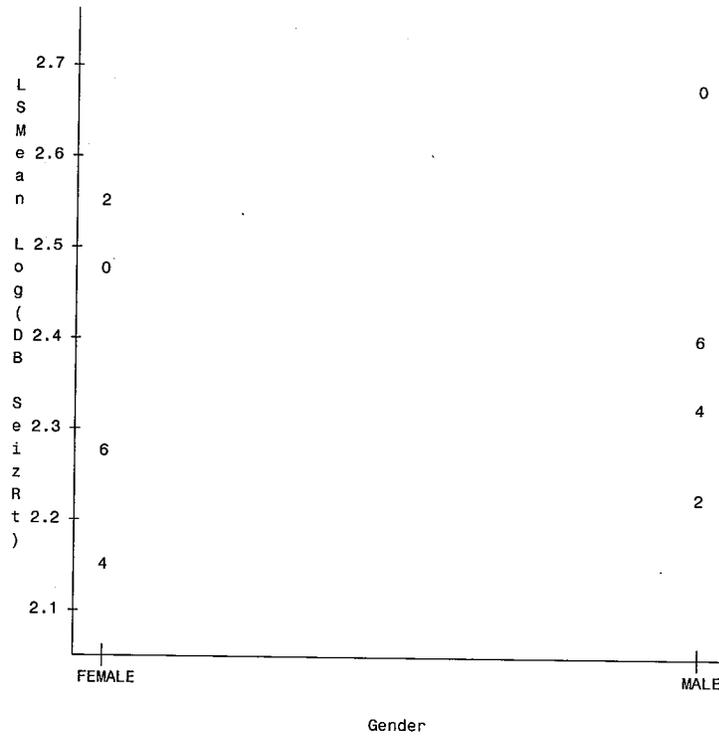
Furthermore, as seen in Table 26, over all of the data it seems that the treatment effect does not depend significantly on gender, at least for the 400 and 600 mg/day groups.

Table 26 Treatment Effect by Gender in Pooled FAS Population (inc. 667,754,755)

SUBGROUP	N	GROUP	MEDIAN BASE SZRATE	MEDIAN PCTCHG	MEAN LOG(BASE SZRATE)	LSMEAN LOG(DB SZRATE)	PCTREDUC* OVER PLACEBO	95% CI	P-VALUE#
Female	174	Placebo	11.4	13.6	2.86	2.54			
	133	LCM 200mg/day	12.5	20.3	2.94	2.52	-2.18	(-19.94; 15.57)	0.8115
	244	LCM 400mg/day	12.5	25.5	2.84	2.34	-17.97	(-30.49; -5.45)	0.0112
	110	LCM 600mg/day	13.0	26.9	2.82	2.38	-15.39	(-31.85; 1.07)	0.0927
Male	185	Placebo	11.0	6.7	2.71	2.48			
	134	LCM 200mg/day	10.5	24.8	2.83	2.22	-23.47	(-35.34; -11.60)	0.0008
	222	LCM 400mg/day	10.4	25.7	2.67	2.24	-21.62	(-32.25; -10.99)	0.0005
	92	LCM 600mg/day	13.5	32.8	2.83	2.18	-26.32	(-39.60; -13.03)	0.0010

Treatment By Gender Interaction test p=   0.3022

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4.1.2 Race

About 90% of patients were Caucasian. The next two largest groups were African Americans with 56 (4.3%) and Hispanics with 32 (2.6%). Based on the limited data for non-Caucasian races there was no compelling evidence that the treatment effect varied significantly with race (p=0.20 comparing treatment effects for Caucasians to treatment effects for others).

4.1.3 Age

The range of ages was fairly constant across the studies. Ages ranged from 18 to 68 in study 667, 16 to 71 in study 754 and 16 to 70 in study 755. The median ages were 40, 38, and 37 respectively. There were only a total of 18 patients age 65 or above, so no reliable analysis of efficacy can be done in this subgroup. A test for a differential effect according to age was not significant (p=0.879) in the pool of the three studies. This test assumed double blind seizure rates were linear in age, allowing for a separate linear relationship for each group. It concluded that the slopes were not significantly different implying that there is insufficient evidence to conclude that the treatment effect varied significantly with age.

4.2 Other Special/Subgroup Populations

4.2.1 Individual Sites and Countries

4.2.1.1 Study 667

There were 65 sites and the average total number of patients per site was just under 8. In the figure below the black symbols show the treatment difference for the 600 mg/day vs. placebo comparison at each site and the blue symbols show the difference for the 400 mg/day vs. placebo comparison. The 200 mg/day vs. placebo comparison is not shown. One can see which sites favored both the middle and the high dose and which did not. Site 5034 (N=13) had one of the larger effects for the 400 mg/day vs. placebo comparison accounting for sample size but excluding the site's data did not change the significance of the primary analysis result. Site 8281 had only 6 total patients but the effects for 400 and 600 mg/day vs. placebo were large. The significance of the result was not changed by excluding data from any site.

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Figure 5 Study 667: Treatment Effects by Site (Excluding 200 mg group)
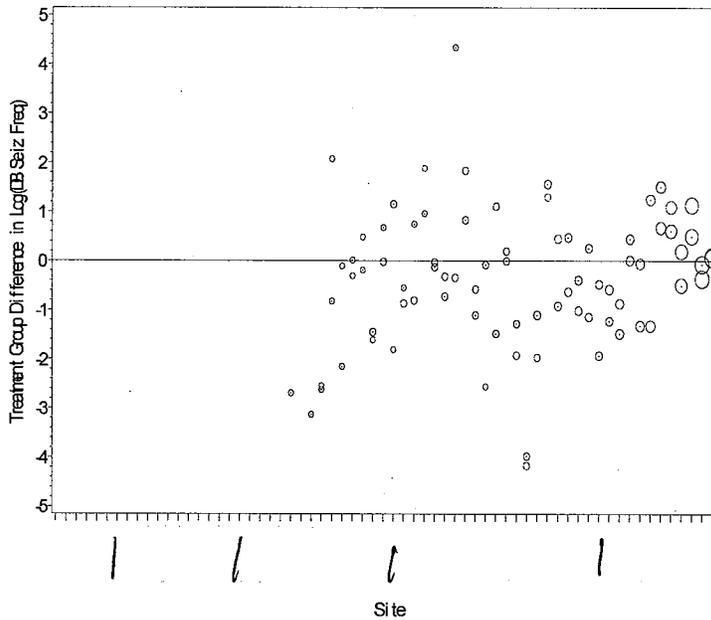
Note: Blue=400 vs. placebo; Black=600 vs. placebo; 200 vs. placebo not shown

4.2.1.2 Study 754

There were 72 sites and the average total number of patients per site was 7. The black symbols in the figure below show the treatment difference for the 600 mg/day vs. placebo comparison and the red symbols show the difference for the 400 mg/day vs. placebo comparison. One can see which sites favored both doses and which did not. Sites 060 (N=18) and 020 (N=10) had two of the larger effects for the 400 mg/day vs. placebo comparison accounting for sample size but separately excluding each of the site's data did not change the significance of the primary analysis result.

Figure 6 Study 754: Treament Effects by Site

Note: Red=400 vs. placebo; Black=600 vs. placebo

4.2.1.3 Study 755

There were 75 sites and the average total sample size per site was 8.5. In the figure the black symbols show the treatment difference for the 400 mg/day vs. placebo comparison and the red symbols show the difference for the 200 mg/day vs. placebo comparison. One can see which sites favored both doses and which did not.

The significance of the result for 400 mg/day vs. placebo was sensitive to the exclusion of some sites such as sites 141 and 181 when small sites were not pooled but it was not if they were, as specified in the analysis plan.

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Figure 7 Study 755: Treament Effects by Site

Note: Red=200 vs. placebo; Black=400 vs. placebo

5   SUMMARY AND CONCLUSIONS

5.1   Statistical Issues and Collective Evidence

Dose Response

In study 667 which included placebo, LCM 200 mg/day, LCM 400 mg/day, and LCM 600 mg/day groups there was slight evidence of dose response between the 200 and 400 groups, but little evidence of a difference in dose response between the 400 and 600 groups. The difference between 200 mg/day and placebo did not reach the nominal level of statistical significance although it did numerically favor the 200 mg/day group (p=0.139).
Note that there was only limited evidence of dose response between the Lacosamide groups. The 400 and 600 mg/day groups had almost the same effects on the double blind seizure rate. The 200 mg/day effect was numerically smaller but there was not a statistically significant difference between it and the other LCM groups (exploratory comparisons: 200 vs. 400, p=0.113; 200 vs. 600, p=0.434). An exploratory test for a linear trend in the double blind seizure rates as a function of the Lacosamide dose (excluding the placebo group) suggested a lack of a significant linear trend (p=0.437).

In study 755 which included placebo, LCM 200 mg/day, and LCM 400 mg/day groups, both LCM groups demonstrated significantly better efficacy than placebo (p=0.0483 for 200 mg/day and 0.0272 for 400 mg/day). There was little evidence of a difference in dose response between

the 200 and 400 groups. An exploratory comparison of the 200 and 400 mg/day groups suggested a lack of a significant difference between them (p=0.819: average monthly seizure rates over the maintenance period were 9.7 and 9.5 for 200 and 400 mg/day, respectively). However, it should be noted that the study was not powered for this comparison.

If we pool the studies together, ignoring the fact that the length of titration was 2 weeks shorter in study 755 and therefore the maintenance period also ended 2 weeks earlier, we find only limited evidence of a difference in dose response between the 200 mg/day and 400 mg/day groups based on the larger combined sample (p=0.391). There is also no very compelling evidence that the within study difference between the 200 and 400 groups depended on the study (p=0.196). The lack of significance of the 200 mg versus placebo comparison in study 667 may have been a power issue as the sample size per group was smaller in that study than in study 755.

Table 27 Pooled Analysis of Double Blind Seizure Rate

GROUP	N	GROUP	MEDBASE	MEDPCTCHG	LOGBASE	LSMNLOGDB	PCTREDUC*	95% CI
Placebo	359	Placebo	11.0	9.9	2.78	2.52		
LCM 200	267	LCM 200mg/day	12.2	22.3	2.88	2.37	-13.86	(- 24.07; -3.65)
LCM 400	466	LCM 400mg/day	11.0	25.6	2.76	2.29	-20.33	(- 28.39; - 12.28)
LCM 600	202	LCM 600mg/day	13.5	27.8	2.83	2.28	-21.27	(- 31.63; - 10.91)

In conclusion, there is only limited and unconvincing evidence of a difference in dose response in terms of the double blind seizure rate between the 200 mg/day and 400 mg/day groups (p=0.196), although the 400 mg group was more consistently statistically significant compared to placebo. There is also almost no difference in efficacy evident between the 400 mg/day and 600 mg/day groups.

5.2   Conclusions and Recommendations

The data from the three phase 3 trials seem to support the efficacy of Lacosamide as adjunctive therapy for partial seizures. The 400 mg/day dose was represented in each study and was statistically significantly better than placebo in each study. The 600 mg/day dose was also significantly better than placebo in the two studies it was included in, but there was no compelling evidence that the 600 mg/day dose provided added improvement over the 400 mg/day dose. The 200 mg/day dose was significantly better than placebo in one of the two studies in which it was included. Although in both studies in which it was included it's effect was numerically smaller than that of the 400 mg/day dose, in one, the difference was very small and, in both studies, the exploratory comparison of the difference between it and the 400 mg/day dose was not nominally significant.

/s/

Tristan Massie
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5/29/2008 03:32:34 PM
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Kooros Mahjoob
6/2/2008 09:49:49 AM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-253/ ⸺ Study SP903	**b(4)**
Drug Name:	Lacosamide	
Indication(s):	Abuse Liability Assessment	
Applicant:	Schwarz Pharm.	
Date(s):	Consult received: March 3 Data received: March 19 Completed: April 1	
Review Priority:	High	
Biometrics Division:	DB VI	
Statistical Reviewer:	Ling Chen, Ph.D. Mathematical Statistician, Special Project Team	
Concurring Reviewers:	Stella Machado, Ph.D. Acting Team Leader, Division Director	
Medical Division:	Controlled Substance Staff	
Clinical Team:	Bonson, Katherine Klein, Michael	
Project Manager:	Moody, Corinne P	

Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Introduction

1.1 Background

The consult for analyzing data from a clinical trial of the human abuse potential of lacosamide was received on March 3, 2008 from the Controlled Substance Staff (CSS) at FDA. However, the dataset for requested analyses was not received until March 18. Therefore, the desired completion date of the consult changed from March 21 to April 10, 2008.

1.2 Data Location

The original submission of study lacosamide was located

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Because data were not well organized for statistical analyses, per the reviewer's request, the applicant resubmitted data on March 18, 2008. The following was the link of the data sets used in this review.

\\Fdsfs01\ode2\Matt\Lacosamide datasets FDA follow-up SP903

2. Statistical Evaluation Potential for Abuse Liability of Lacosamide

2.1 Study design and endpoints

This was a single-site, randomized, double-blind, placebo- and active comparator-controlled crossover Phase I trial in healthy male and female subjects with a history of recreational central nervous system (CNS) depressant use to assess the abuse potential of lacosamide.

The trial was conducted at a single trial site in Canada.

The trial consisted of an initial Qualification Phase (QP) and a main Treatment Phase. Subjects fulfilling all of the inclusion and none of the exclusion criteria at Eligibility Assessment (EA) entered the pre-testing QP within 30 days thereafter. The QP consisted of a 4-day In-house Phase. Subjects were randomized prior to first dosing to a double-blind crossover treatment of the following on 2 consecutive days:

- Single oral administration of placebo

- Single oral administration 2 mg alprazolam (positive control drug)

Only subjects who demonstrated the ability to distinguish the positive control drug from placebo were qualified for the main Treatment Phase.

Lacosamide is rapidly and completely absorbed after oral administration and has minimal protein binding properties, thus reducing the risk of displacement drug-drug interactions. The time to peak plasma concentrations (tmax) is between 0.5 to 4 hours post-dose. Plasma half-life of the unchanged drug is approximately 13 hours and is not altered by different doses or by multiple dosing. The plasma half-life of alprazolam is approximately 8-20 hours. During the main Treatment Phase, subjects received the following treatments in a randomized double-blind order, separated by a Wash-Out Period of at least 5 but no more than 9 days between each drug administration, as that the trial consisted of 5 treatment periods for each subject:

- Single oral administration of 200 mg lacosamide
- Single oral administration of 800 mg lacosamide
- Single oral administration of 1.5 mg alprazolam (positive control drug)
- Single oral administration of 3 mg alprazolam (positive control drug)
- Single oral administration of matching placebo

Reviewer's comments: The wash-out period of the study is adequate.

The following five treatment sequences were used in the study.

A B E C D
B C A D E
C D B E A
D E C A B
E A D B C

Where A=200 mg lacosamide (L200), B=800 mg lacosamide (L800), C=1.5 mg alprazolam (A1.5), D=3 mg alprazolam (A3), and E=Placebo (P).

Reviewer's comments: The sponsor did not mention the reason for selecting these sequences. It is obviously not a Williams design.

The primary endpoints for this trial were the following:

<u>Drug Liking VAS</u>

The Drug Liking VAS assesses the response to the question "At this moment, my liking for this drug is." Values for this scale can range from 0 (strong disliking) to 100 (strong liking) with 50 representing a "neutral" value.

Reviewer's Comments: Using a positive number to assess disliking is not proper. The scale should be modified to from -50 to 50. Zero represents "neutral".

Overall Drug Liking VAS

The overall drug liking VAS assesses the response to the question "Overall, my liking for this drug is," asked at the end of the day (12 hours) and the next day (24 hours postdose).

Reviewer's Comments: The same as the comments on Drug Liking.

Subjective Effects VAS: High

The Subjective Effects VAS: High assesses the response to the question "I am feeling high." Values can range from 0 (definitely not) to 100 (definitely so).

ARCI: PCAG scale

The ARCI PCAG is a measure of sedation. Values for the ARCI PCAG can range from 0 (no sedation) to 15 (strong sedation).

There are many secondary PD variables and supportive PD variables proposed by the sponsor. In this review, the reviewer examined the following PD variables per the CSS's request:

Take Drug Again VAS

The Take Drug Again VAS assesses the response to the question "I would take this drug again" (asked at 12 and 24 hours postdose). Values for this scale can rang from 0 (definitely not) to 100 (definitely so).

ARCI: MBG

The ARCI MBG is a measure of euphoria. Values can range from 0 (no euphoria) to 16 (strong euphoria).

VAS: Good Drug Effects

Good Drug Effects assess the response to question "I can feel good drug effects". Values for this scale can range from 0 (definitely not) to 100 (definitely so).

VAS: Bad Drug Effects

Bad Drug Effects assess the response to question "I can feel bad drug effects". Values for this scale can range from 0 (definitely not) to 100 (definitely so).

2.2 Participants

2.2.1 Participant characteristics

The study subjects were healthy males and females with a history of recreational central nervous system (CNS) depressant use. Among 38 subjects randomized, ages ranged from 20 to 44 with a mean 33.1 and a standard deviation 7.4. There were 3 Asian (7.9%), 4 Black (10.5%), 29 White (76.3%) and 2 other (5.3%) subjects. The majority subjects were males (73.7%).

2.2.2 Participant disposition

Seventy-six subjects were randomized to the QP of the trial. Of these, 73 subjects completed the QP and 3 subjects discontinued early. Thirty-eight of the 73 subjects were eligible for the main Treatment Phase and 35 subjects were classified as run-in failures. The 38 subjects eligible for the main Treatment Phase were randomized to 5 different treatment sequences. Eight out of 38 subjects were discontinued early. Their information is listed in Table 1 below:

Table 1: Summary of Subject Disposition

SubjID	Treatment Completed	Reason for Discontinue
80021	A-B-E-C	Consent withdrawn
80033	A-B	Unsatisfactory compliance
80011	B-C	Other reasons
80023	B-C-A-D	Consent withdrawn
80020	C	Other reasons
80006	D-E	Unsatisfactory compliance
80004	E-A-D	Consent withdrawn
80029	E-A	Other reasons

Note: Treatment key: A=200 mg lacosamide; B=800 mg lacosamide; C=1.5 mg alprazolam; D=3 mg alprazolam; E=placebo

The study report noted that 11 subjects were allowed to participate even though they did not meet criteria for the Treatment Phase. The breakdown cases are:

- Six subjects did not have a peak score on the Overall Drug Liking variable analog scale (VAS) in response to 2 mg alprazolam that was greater than that of placebo.
- four subjects did not have "an appropriate pharmacological response on 7 measures"

- One subject failed to qualify on either peak score on Overall Drug Liking or on
- "appropriate pharmacological response".

The number of subjects taking each treatment sequence is listed below:

A-B-E-C-D (N=7, completed n=5)
B-C-A-D-E (N=8, completed n=6)
C-D-B-E-A (N=8, completed n=7)
D-E-C-A-B (N=7, completed n=6)
E-A-D-B-C (N=8, completed n=6)

Reviewer's comments: It can be seen that although 30 can be divided by 5 evenly, sequences taking by subjects are not balanced.

2.3 Statistical methodologies

2.3.1 Statistical analyses (Protocol-Defined)

A mixed-effect model, including sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect for a crossover trial was used by the Sponsor to calculate pairwise mean differences (least squares means [LSMeans]) and the respective 2-sided 95% confidence intervals (CIs). The maximum effect Emax was derived for each period for all PD variables by calculating the maximum value of each period. Emax for Subjective Effects VAS and the ARCI scales was analyzed using an analysis of covariance (ANCOVA) analogously to the ANOVA model, with the Baseline value of Subjective Effects VAS: High included in the model as a covariate.

Reviewer's comments: It is not clear to the reviewer how the baseline value was defined. Was baseline a measurement taken before the Treatment Phase or a predose observation before a drug session? In this reviewer's opinion, change from predose Emax should be considered as a response variable in the model to reduce possible carryover effect. In addition, High VAS is not the only variable that had predose observations.

The following contrasts were calculated:

- Response to each dose of alprazolam compared to response of placebo
- Response to each dose of lacosamide compared to single and multiple response of placebo (eg, mean response to lacosamide compared to 2 times mean response of placebo)
- Response to each dose of lacosamide compared to response of each dose of alprazolam

For each comparison, the 2-sided 95% CI and the p-values for the differences of the mean responses were calculated.

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The Sponsor considered the trial to be valid if on at least 3 of 6 endpoints (Drug Liking VAS, Overall Drug Liking VAS, ARCI MBG, ARCI PCAG, Good Drug Effects VAS, and Subjective Effects VAS: High), the 95% CI of differences of the Emax of either dose of alprazolam and placebo did not included zero, and a non-descending dose-response was observed.

2.3.2 Changes to the planned analysis by the sponsor

The sponsor reported:

It was planned to calculate comparisons for multiple responses from placebo (2-times placebo or 3-times placebo) to lacosamide. Since the PD variables for "Drug liking" and "Overall drug Liking" are bipolar scales with range from 0 (=strong disliking) to 100 (=strong liking), the placebo responses were somewhere in the neutral range (=50). This neutral range was not adequately addressed in the calculation of the multiple responses and resulted in values above the measurable scale. Therefore, a scale-adjusted calculation of these responses was done in addition to the original analysis. Values above 0 can then be interpreted as a response in the liking range, while values below 0 can be interpreted as a response in the disliking range. With this scale adjustment, the comparison between the 2-times or 3-times placebo response and the response to both doses of lacosamide is within the measurable scales and can be interpreted.

Reviewer's comments: The disadvantage to use range from 0 (=strong disliking) to 100 (=strong liking) for Drug Liking and Overall Drug Liking is obvious. However, the sponsor did not provide a good solution for the problem with the scale used for Drug Liking and Overall Drug Liking. Separating responses from Drug Liking (Overall Drug Liking) into two parts according to the sign of difference between original responses and the neutral number 50 reduced the sample size greatly for assessing either Drug Liking (Overall Drug Liking) or Drug disliking (Overall Drug Disliking). Therefore, the power of the planned tests was not preserved. After subtracting 50 from original responses to those endpoints, we should be able to assess Drug Liking and Overall Drug Liking directly using the adjusted data. The negative values in responses have been taken into account for drug disking.

2.3.3 Statistical analyses by the reviewer

2.3.3.1 Study model

Emax of responses of primary and secondary variables were used in the reviewer's analyses except variables High VAS, ARCI PCAG, and ARCI MBG, for which change from predose Emaxs were used.

A mixed linear model with period, treatment, sequence and first-order-carryover as fixed effects and subject nested within sequence as a random effect was used in the reviewer's

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analyses. If the first-order-carryover effect is not statistically significant at $\alpha = 0.25$, this term was dropped from the model. If the responses as modeled did not appear to be normally distributed, then ranks of responses within subjects were used in the statistical analysis.

2.3.3.2 Evaluation procedure

In order to claim there is no potential for abuse liability of lacosamide, for each primary variable the data should provide sufficient evidence that

- Each dose of alprazolam has statistically larger mean response than placebo (to insure the validity of alprazolam as the positive control.)
- Each dose of lacosamide has statistically lower mean response than double the mean response of placebo
- Each dose of lacosamide has statistically lower mean response than all doses of alprazolam.

The given significance level of each test is 5% (two-sided).

More specifically, for each primary variable, tests of the following null hypotheses were performed:

- the mean response of 1.5 mg (or 3 mg) alprazolam is equal to that of placebo
- the mean responses to 200 mg, and 800 mg lacosamide are greater than or equal to double the mean response of placebo
- the mean response of 1.5 mg (or 3 mg) alprazolam is less than or equal to that of 200 mg and 800 mg lacosamide.

The same procedure was used to evaluate the secondary variables suggested by the CSS.

2.4 Results and conclusions

2.4.1 Sponsor's results and conclusions from Study SP903

Results from the Sponsor's statistical analyses were based on the normal assumption of the study model. However, the residuals to all PD variables under the CSS's concern as modeled did not appear to be normally distributed except ARCI PCAG. Therefore, most statistical analyses by the Sponsor were incorrect. In addition, in this reviewer's opinion, the Sponsor analyzed Drug Liking and Overall Drug Liking incorrectly (see reviewer's comments on page 8). Therefore, the Sponsor's results are not presented in this report, but one may find those results in Chapter 8 in the Sponsor's report.

The Sponsor stated in their report:

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Any conclusion regarding the abuse liability of the drugs also considered the medical judgment of statistical results in the whole setting. Although measures were separated into primary, secondary, and supportive variables, conclusions regarding the abuse liability of the drugs considered the whole profile of subjective effects across all of the primary, secondary, and supportive measures, and not responses on individual scales.

2.4.2 Descriptive statistics and interpretations from the reviewer

The reviewer's analyses were based on 30 completers. Tables 2 and 3 listed mean, standard deviation (Std), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), maximum (Max), and range for each treatment by each primary variables and by each secondary variables respectively. These two tables were based on original observations, except Drug Liking and Overall Drug Liking. For Drug Liking and Overall Drug Liking, adjusted data (by subtracting 50 from the original responses) were used. The adjusted data ranged from -50 to 50. The negative values indicate degrees of disliking, and zero indicates neutral.

Table 2: Summary statistics for Emax or Change from Pre-dose Emax (I) (Primary Variables)

Endpoint	Treatment	N	Mean	Std	Min	Q1	Med	Q3	Max	Range
Drug Liking	P	30	4.13	11.70	-24	1	1	2.25	50	74
Drug Liking	L200	30	13.37	14.59	-2	1	10	19	50	52
Drug Liking	L800	30	23.20	21.27	-35	13.75	24	40	50	85
Drug Liking	A1.5	30	29.33	14.07	1	20.75	30	42.25	50	49
Drug Liking	A3	30	35.57	16.13	-23	29.5	39	50	50	73
High	P	30	14.37	26.07	0	0	0	16	100	100
High	L200	30	52.47	32.81	0	34	57	70.5	100	100
High	L800	30	82.17	20.17	9	69.5	88.5	100	100	91
High	A1.5	30	78.83	22.67	9	70.5	80.5	98	100	91
High	A3	30	87.83	12.05	65	78.75	91.5	100	100	35
Overall Drug Liking	P	30	-2.27	18.14	-50	-1.5	0	1	50	100
Overall Drug Liking	L200	30	3.73	22.66	-50	0	2.5	19.5	42	92
Overall Drug Liking	L800	30	-5.37	35.07	-50	-50	0	20	50	100
Overall Drug Liking	A1.5	30	26.87	24.60	-50	13.75	32	46.5	50	100
Overall Drug Liking	A3	30	32.43	21.97	-50	25.5	39.5	50	50	100
PCAG Scale	P	30	1.30	2.28	-2	0	1	2	8	10
PCAG Scale	L200	30	2.03	2.30	0	0	1	3.25	8	8
PCAG Scale	L800	30	7.77	2.69	1	6	8	10	12	11
PCAG Scale	A1.5	30	6.87	2.18	2	5	7	8	11	9
PCAG Scale	A3	30	7.27	2.68	2	5	7	9	13	11

It can be noticed from Table 2 that the third quartile of placebo responses to each primary variable is much smaller than that of other treatments except L200 in PCAG Scale. That

means approximately 75% subjects identified placebo treatment. The mean response of each dose of lacosamide is between those of placebo and alprazolam for all primary variables except that of L800 in responding to Overall Drug Liking and High. The first quartile of responses to Overall Drug Liking in L800 group was -50. That means approximately 25% of subjects strongly disliked L800. It can also be noticed that approximately 25 % of subjects had strong bad drug effects with a response 100 in L800 group (See Table 3).

Table 3: Summary Statistics for Emax or Change from Pre-dose Emax (II)
(Secondary Variables)

Endpoint	Treatment	N	Mean	Std	Min	Q1	Med	Q3	Max	Range
Bad Drug Effects	P	30	15.33	25.17	0	0	0	43	75	75
Bad Drug Effects	L200	30	25.17	28.84	0	0	7	50.25	83	83
Bad Drug Effects	L800	30	66.37	30.8	0	50	69	100	100	100
Bad Drug Effects	A1.5	30	29.07	25.12	0	6.75	20	50	100	100
Bad Drug Effects	A3	30	41.27	27.25	0	12.5	47	67.25	91	91
Good Drug Effects	P	30	35.63	29.92	0	0	48.5	51.25	100	100
Good Drug Effects	L200	30	56.7	29.82	0	50	58	73.5	100	100
Good Drug Effects	L800	30	73.63	25.99	0	61.75	74	100	100	100
Good Drug Effects	A1.5	30	82.27	17.17	28	71	84.5	98.5	100	72
Good Drug Effects	A3	30	88	13.21	51	82.25	90.5	100	100	49
MBG Scale	P	30	0.7	1.622	-2	0	0	1	7	9
MBG Scale	L200	30	2.167	3.384	0	0	1	2.5	13	13
MBG Scale	L800	30	3.967	5.136	0	0	1.5	6.25	15	15
MBG Scale	A1.5	30	4.333	3.827	0	2	3	6	14	14
MBG Scale	A3	30	6.133	3.937	0	2.75	6	9	15	15
Take Drug Again	P	30	39.3	27.36	0	7.5	50	51	100	100
Take Drug Again	L200	30	58.63	32.19	0	37.25	60	83.75	100	100
Take Drug Again	L800	30	44.8	38.77	0	0	39.5	81.5	100	100
Take Drug Again	A1.5	30	85.73	24.31	0	77.25	99	100	100	100
Take Drug Again	A3	30	86.87	20.31	0	78	93	100	100	100

The following Figure 1, scatter plot matrix, shows the linear relationships among variables Take Drug Again, Overall Liking, Bad Drug Effects and High at VAS scale. The sample correlation coefficients are listed in Table 4.

From Figure 1, it can be seen that Overall Drug Liking is highly correlated with Take Drug Again (r = 0.9033). The correlations between Overall Drug Liking and High (r = 0.2927), and between Take Drug Again and High (r = 0.1649) are very small. Moderate negative correlations were observed between Bad Drug Effects and Overall Drug Liking (r = -0.5507), and between Bad Drug Effects and Take Drug Again (r = -0.4879).

From the scatter plot of Overall Drug Liking and Bad Drug Effects, one may notice that most subjects who had high response in responding to Bad Drug Effects had negative

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values or values near zero in responding Overall Drug Liking. In some sense those bad drug effects have been taken into account in evaluation of Overall Drug Liking.

Figure 1: Scatter Plot Matrix for Four VAS Variables
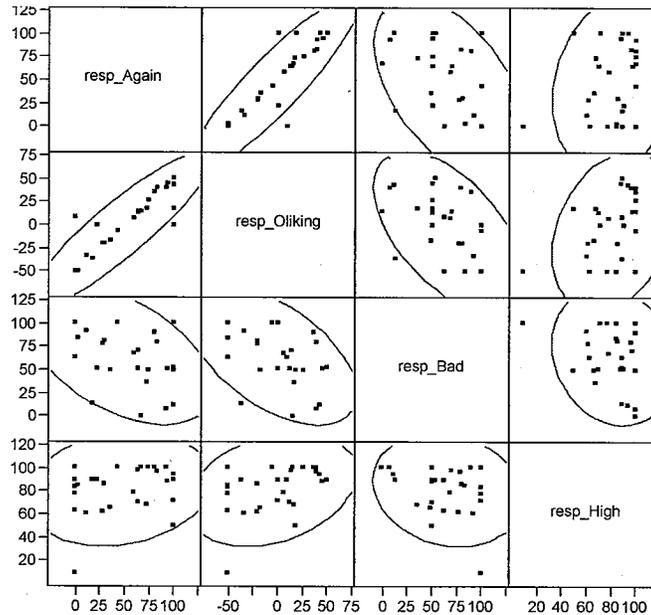
Table 4: Multivariate Correlations

	Take Drug again	Overall Drug Liking	Bad Drug Effects	High
Take Drug Again	1.0000	0.9033	-0.4879	0.1649
Overall Drug Liking	0.9033	1.0000	-0.5507	0.2927
Bad Drug Effects	-0.4879	-0.5507	1.0000	-0.1630
High	0.1649	0.2927	-0.1630	1.0000

Table 5: Responses from Patient ID 80031

PD Variable	A1.5	A3	L200	L800	P	Scale
Bad Drug Effects	100	71	0	100	0	0 to 100
Drug Liking	21	25	1	23	0	-50 to 50
Good Drug Effects	67	68	0	63	0	0 to 100
High	100	100	0	71	0	0 to 100
MBG Scale	0	7	0	0	0	0 to 16
Overall Drug Liking	-9	-7	0	0	0	-50 to 50
PCAG Scale	11	8	0	10	0	0 to 15
Take Drug Again	100	75	89	100	51	0 to 100

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From the scatter plot of Take Drug Again versus Bad Drug Effects, one may notice that one subject had a response 100 to both Bad Drug Effects and Take Drug Again. The subject had a patient ID 80031. All responses from this subject are listed in Table 5. From this patient's responses to eight PD variables and five different treatments, it is easy to see that this patient can identify placebo and positive control drug. This patient gave a 100 to Bad Drug Effects and moderate high responses to VAS Drug Liking, Good Drug Effects, High and ARCI PCAG when taking L800. This patient gave a neutral response to Overall Drug Liking of L800. Despite bad drug effects, the patient still strongly wanted to take L800 again.

From this case, one should notice that the bad drug effects may not necessarily push drug abusers away from the drug.

3.4.3 Results from the reviewer's inferential statistical analyses

SAS proc mixed was used to evaluate the significance of the fixed effects, and Shapiro-Wilk W-test in SAS proc univariate was used to assess the normality assumption of the study model. It was found that residuals of the model for all PD variables of interest except ARCI PCAG had significant non-normal distributions, thus ranks of responses within subjects were used in the statistical analysis for those variables.

The first-order carryover effects were not significant in all modeled PD variables at 25% significance level. Therefore, this term was dropped in all models for assessing PD variables.

Although Sequence and Period effects were also not significant, because of the Latin square design, the reviewer kept those terms in the final study model.

Table 6 gives one sided p-values of the pairwise comparisons of treatments for eight PD variables: Drug Liking (Liking), Overall Drug Liking (O Liking), High, PCAG, Take Drug Again (Again), Good Drug Effects (Good), Bad Drug Effects (Bad) and MBG. The first column denotes the alternative hypotheses in comparisons. A number in red ink shows that the test was statistically significant at 2.5% level (one-sided) in an opposite direction of the alternative hypothesis. A number in blue ink shows that the test is not significant at 2.5% level (one-sided). Comparisons between L200 and 2P, and between L800 and 2P were used Wilcoxon signed rank test except for PCAG, which used a paired t-test. Besides the necessary comparison on such a study, the reviewer also put the comparison between each dose of lacosamide and placebo in the table. From Table 6 one may see that the trial was well validated. The analysis showed that L200 had significantly lower median (or mean) response than both A1.5 and A3 for all PD variables except for Bad Drug Effect in comparison between L200 and A1.5. Tests failed to demonstrate that the median (or mean) response in L200 was significantly lower than double the median (or mean) response of placebo. For High VAS, the test showed a median response of L200 was significant larger than double the median response of Placebo. In 16 comparisons between L800 and two doses of alprazolam for eight PD variables, only six out of 16 cases show significant results. Notice that the p-values in comparison between

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L800 and 2P were greater than 0.9750 in Drug Liking, High, PCAG and MBG. That means the tests showed that median (or mean) responses of L800 to these four PD variables were significantly higher than double the median (or mean) responses of Placebo. It should be notice that in comparisons with L800, Take Drug Again passed all requested comparisons with positive control drug and placebo. On the other hand, in comparisons between L800 and two doses of alprazolam, and between L800 and 2P, Bad Drug Effects showed significant results in the opposite direction of the alternative hypotheses.

Table 6: Pairwise Comparisons of Treatments: p-values (one-sided)

Comparison	Primary Endpoint				Secondary Endpoint			
Alternative Hypothesis	Liking	O Liking	High	PCAG	Again	Good	Bad	MBG
P < A1.5	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0013	<.0001
P < A3	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Validation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
L200 < A1.5	<.0001	0.0001	<.0001	<.0001	<.0001	<.0001	0.0452	0.0002
L200 < A3	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0002	<.0001
L200 > P	0.0094	0.0872	0.0002	0.1916	0.0073	0.0960	0.1971	0.0238
L200 < 2P	0.9731	0.9226	0.9934	0.2750	0.0575	0.0079	0.1071	0.8505
L200 abuse potential*	Maybe	Maybe	Maybe	Maybe	Maybe	No	Maybe	Maybe
L800 < A1.5	0.1597	<.0001	0.1319	0.9503	<.0001	0.1555	1.0000	0.0473
L800 < A3	0.0008	<.0001	0.2073	0.8145	<.0001	0.0314	0.9998	0.0011
L800 > P	<.0001	0.2573	<.0001	<.0001	0.0960	<.0001	<.0001	<.0001
L800 < 2P	0.9970	0.3679	0.9999	1.0000	0.0031	0.7289	0.9998	0.9920
L800 abuse potential*	Maybe	Maybe	Maybe	Maybe	No	Maybe	No	Maybe

Note:
1. A number in red ink shows that the tests was statistically significant at alpha=0.025 in an opposite direction of the alternative hypothesis.
2. A Number in blue ink shows that the test was not statistically significant at alpha=0.025.
3. Tests except for PCAG are based on ranks due to failing to satisfy the normal assumption in the study model.
4. The comparisons between L200 and 2P, and between L800 and 2P used Wilcoxon signed rank test except for PCAG which used a paired t-test.
* Based on the criteria on page 9.

Detailed SAS results are listed in Appendix I and II.

Figures 2 and 3 are box plots of responses on the eight PD variables. From those boxplots one may see a rough distribution of responses to each treatment by each PD variables.

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Figure 2: Boxplots for Primary Variables

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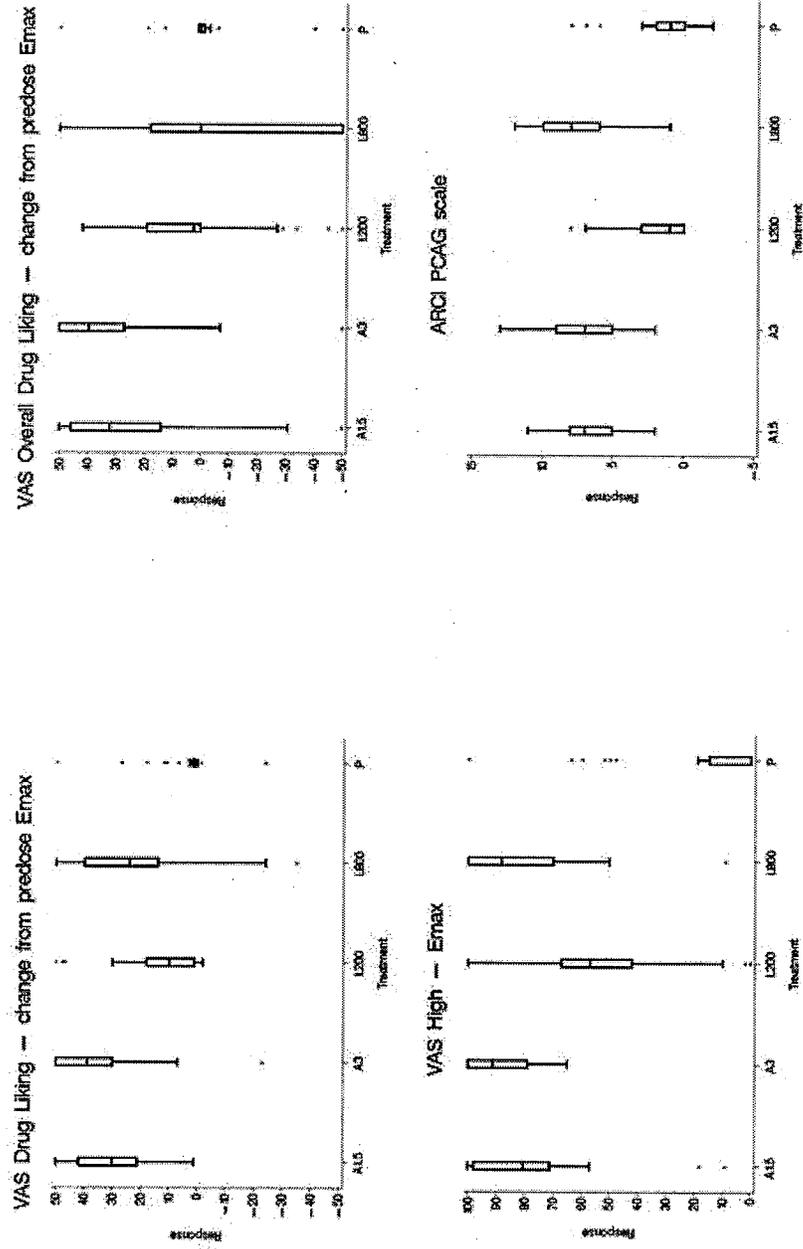
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Figure 3: Boxplots for Secondary Variables
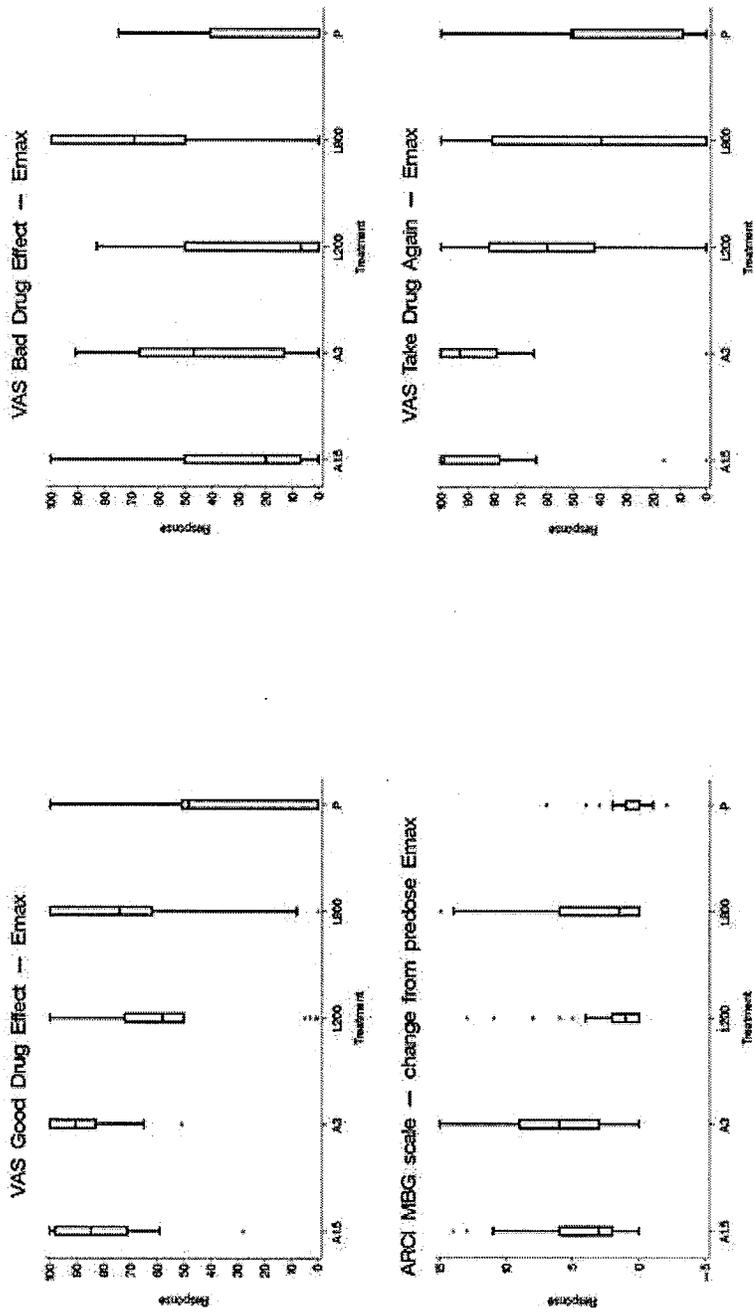
3. Discussion and Conclusion

3.1 Discussion

Although the Sponsor did not perform satisfactory statistical analyses, the study was designed relatively well compared to other studies that have been seen by this reviewer. The Qualification Phase was successful. It is evident by significant results obtained from all validation tests for all PD variables interested by the CSS.

Even though for many PD variables the median (or mean) responses from L800 and L200 were significantly smaller than that of each dose of positive control drug, only the PD variable Take Drug Again passed the test that compared with double the median response of Placebo. It has been noticed that the median response in L800 group on Bad Drug Effects was significantly higher than those in alprazolam groups, and was also significantly higher than double the median response of placebo on Bad Drug Effects. One might interpret this scenario as approximate 50% of subjects did not want to take L800 again because of bad drug effects. However, from the case with Patient ID 80031 discussed in Session 2.4.2 earlier, we know that such an interpretation may be incorrect.

3.2 Conclusion

The reviewer's analyses show that Study SP903 was not a negative study in terms of drug abuse potential, because based on the criteria on page 9 L200 only passed all tests for Good Drug Effects, and L800 only passed all tests for Take Drug Again and Bad Drug Effects. In addition, the median (or mean) response in L800 group was significantly larger than double the median (or mean) response in placebo group for three out of four primary variables VAS Drug Liking, VAS High, and ARCI PCAG, and secondary variable ARCI MBG.

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_____✓_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDY

NDA Number:	22,253 / Serial 000
Drug Name:	Lacosamide® Tablets (also referred to as SPM-927) [(R)-2-acetamido-N-benzyl-3-methoxypropionamide Tablets at 50, 100, 150, 200, 250, and 300 mg]
Indication:	1. For adjunctive therapy in the the treatment of partial-onset seizures in patients with epilepsy 16 years and older.
	2. For the management of neuoropathic pain associated with diabetic peripheral neuropathy.
Applicant:	Schwarz BioSciences Inc.
	8010 Arco Corporate Drive, Suite 1000
	Raleigh, NC 27617
Date:	Submitted 09/28/2007
Review Priority:	Standard
Biometrics Division:	Division 6
Statistical Reviewer:	Steve Thomson
Concurring Reviewer:	Team Leader: Karl Lin, Ph. D.
Medical Division:	Neurology Products
Toxicologist:	Reviewers: Ed Fisher, Ph.D.
	Terry Peters, D.V.M.
	Team Leader: Lois Freed, Ph.D.
Project Manager:	Jacqueline Ware, Pharm. D.
Keywords:	Bayesian analysis, Carcinogenicity, Cox regression, Kaplan-Meier product limit, Survival analysis, Trend test

Table of Contents

1. EXECUTIVE SUMMARY

According to the reports provided by the Contract Research Organization, this submission was intended to assess the carcinogenic potential of daily oral administration of compound SPM 927 (Lacosamide®), administered for periods of up to 104 weeks in both mice and rats. The sponsor was Schwarz BioSiences in Monheim, Germany. Both the rat study and the mouse study were conducted by the The descriptions of the studies below are taken from the corresponding final reports.

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1.1. Conclusions and Recommendations

This submission summarizes the results of both a mouse study and a rat study of the carcinogenic potential of SPM 927 (Lacosamide®) following daily gavage for two years. In the rat study there were five treatment groups per gender, with a negative control (tap water), vehicle control, and 40, 80, and, initially 160 mg/kg/day, each with nominally 50 animals per gender. The vehicle was 0.5% aqueous hydroxypropyl-methylcellulose gel. In the 160 mg/kg/day dose group in females, dosages were increased to 180 and later to 200 mg/kg/day (please see Section 3.2.1 for details). The similar mouse study also had five treatment groups per gender with an analogous negative control, and four further dose groups at dosages of 0 (vehicle control), 20, 60, 180 mg/kg/day, again, each with 50 animals. In both studies the five dose groups per gender were labeled as Control 0 (i.e. negative control), Control 1, Low, Medium, and High dose groups, respectively. Note the Sponsor also labels these as dose groups 1 to 5, respectively. Data for one female rat in the High dose group seems to be missing from the data set provided by the Sponsor. So this treatment group has only 49 animals. The remaining dose groups in both genders in both species each have data for 50 animals.

The statistical significances of the tests of differences in survival across treatment groups are given in Table 1 below. The test for homogeneity is a test that survival is equal across treatment groups, while the test of trend is a test of dose related trend.

Table 1: Statistical Significances of Tests of Homogeneity and Trend in Survival

	Rat Males		Females		Mice Males		Females	
	Cox	K-W	Cox	K-W	Cox	K-W	Cox	K-W
Homogeneity over all five groups	0.3054	0.2245	0.4413	0.4996	0.8053	0.8509	0.0845	0.1028
Homogeneity over the Lac. groups	0.2962	0.2205	0.2983	0.3546	0.7031	0.7385	0.0772	0.1205
Trend over Lac. groups	0.2856	0.1612	0.0866	0.1121	0.6782	0.4416	0.8517	0.6303
Departure from trend	0.2786	0.2943	0.6898	0.6955	0.5384	0.7159	0.0333	0.0610

Note that the Cox test is usually called the logrank test, while the K-W, i.e., Kruskal-Wallis test, is more commonly called the Wilcoxon test or the generalized Wilcoxon test. Note that the Wilcoxon test places more weight on earlier events than does the logrank test.

For both species and genders the hypotheses of homogeneity in survival over the five treatment groups was never rejected at the usual 0.05 level (all eight $p \geq 0.0845$). Results were similar when testing homogeneity over the four Lacosamide groups (including the vehicle group) (all eight $p \geq 0.0772$), although results were fairly close to statistical significance in the Cox test in female mice for both tests over all five groups and the subset of four groups. There was no strong evidence of a trend in mortality over the four Lacosamide groups (including the vehicle group) (starting from the vehicle control), although the Cox test in female rats was close (Cox $p=0.0866$). The only statistically significant test in the table is the test of departure from linear trend in female mice (Cox $p=0.0333$). Absence of proof is not proof of absence, but this, and the results on trend, are consistent with the notion of no strong evidence of a dose related trend in survival. Mortality is summarized in tables in Sections 3.2.1.2 and 3.2.2.2. For the Sponsor's assessments (please see Sections 3.2.1.1 and 3.2.2.1). Results from an experimental Bayesian analysis of mortality are summarized in Appendix 2.

The endpoint used in the FDA analyses of tumorigenicity is the minimum of the time of observation, time of death due to the tumor, or time of detection when the animal dies or is sacrificed. To adjust for the multiplicity of comparisons involved in a tumorigenicity analysis for standard rodent models, the Agency analysis follows the Haseman-Lin-Rahman rules described in Section 1.3.1.4 below. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors (background incidence <1%) should be tested at a 0.025 (2.5%) significance level and common tumors at a 0.005 (0.5%) level. Tests of pairwise differences between controls and the highest dose should be tested at a 0.05 (5%) level for rare tumors and at a 0.01 (1%) level for common tumors.

Table 2 below shows the potentially significant results in both studies. However, only results in the rat study fit this criterion. Based on the incidence in the negative control (water only) group, these would all be classified as common tumors. Adjusting for multiplicity using the Haseman-Lin-Rahman rules above, the tests of trend in tumor hair follicles and Leydig cell bilateral adenoma in male rats were not statistically significant (since both $p=0.0430$ and $p=0.0503 > 0.005$). Interestingly, in many studies one would use the vehicle control to assess baseline incidence. In that case, each of the tumors listed below would be classified as rare tumors. However, even if classified as rare tumors, in male rats neither of the two tests of trend would be considered to be statistically significant. In female rats, unilateral C cell carcinoma was also not statistically significant (since $p = 0.0182 > 0.005$). In this case, however, if the tumor was classified as rare, as suggested by the vehicle control, the tumor would be assessed as statistically significant (since $p = 0.0182 < 0.025$). Complete incidence tables are given in Appendix 3. As noted above, in mice, in both genders, no tests of trend or pairwise comparisons were even nominally statistically significant at the usual 0.05 level, let alone after adjustment for

multiplicity using the Haseman-Lin-Rahman rules. Hence no results in mice are displayed in Table 2 below.

Table 2: Potentially Statistically Significant Tumorgenicity Results

	Incidence:					p-values:	
	Ctr0	Ctrl	Low	Med	High	Trend	Hi vs Ctrl
Male Rats							
Lesion (skin back)							
TUMOUR HAIR FOLLICLE	1	0	0	0	2	0.0430	0.1992
Testicle							
ADENOMA LEYDIG CELL bilat	3	0	0	2	2	0.0503	0.2096
Female Rats							
Thyroids							
C CELL CARCINOMA unilat	1	0	0	0	3	0.0182	0.1324

1.2. Brief Overview of the Studies

One mouse study and one rat study were submitted:

Study Report 13295/00 104-Week Carcinogenicity Study by SPM 927 by Oral Administration to CD® Rats,

and,

Study Report 13124/00 104-Week Carcinogenicity Study by SPM 927 by Oral Administration to CD-1 Mice,

These studies were designed to assess the neoplastic potential of SPM 927, i.e., Lacosamide, when administered by once daily oral gavage at dose levels of 40, 80, and 160 mg/kg/day in CD® rats, with the high dose increasing to 180 mg and finally to 200 mg in female rats. The structurally similar study in CD-1 mice was at dose levels of 20, 60, or 180 mg/kg/day. In addition, in each study there was a tap water negative control and a vehicle control group, labeled Control 0 and Control 1, respectively. In each study, the three Lacosamide dose groups were labeled as Low, Medium, and High, respectively. The Sponsor indicates that each of the five treatment groups per gender in each study started with 50 animals. However data for one female rat in the High dose group was not included in the data provided by the Sponsor. It was felt that one animal would not make a difference in results.

1.3. Statistical Issues and Findings

1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include details of the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

1.3.1.1. Survival Analysis:

Both the Cox logrank and Kruskal-Wallis-Wilcoxon tests were used to test homogeneity of survival among the treatment groups. Tests of dose related trend using a Cox proportional odds model were also performed. The number of such tests raises issues of multiple testing, but from the point of view of finding differences among treatment groups (i.e., reducing the probability of Type II error), this should be acceptable. Appendix 1 reviews the animal survival analyses in some detail. The Sponsor's analyses are summarized in Sections 3.2.1.1 and 3.2.2.1. The Sponsor used Fisher exact tests to compare the proportions who survive to Week 104. The Sponsor also indicates that Fisher exact tests were used to compare mean survival times across groups, but provides no details of the analysis. This may refer to permutation tests, but without details, this reviewer has difficulty in understanding this analysis. Appendix 2 includes an experimental Bayes approach to the analysis of mortality performed by this reviewer.

1.3.1.2. Tests on Neoplasms:

The FDA tumorigenicity analyses are essentially those proposed by Peto, et al (1980). The analysis of fatal tumors is based on the time of death, and for observable tumors on time of detection. Both are analyzed at the time of detection with an analysis equivalent to the death rate method. Non-fatal tumors found at the time of the animals' death are labeled as incidental, and were analyzed by the so-called prevalence method. For the FDA analyses all three results were pooled. The tests on these neoplasms used in the FDA analysis are basically tests of trend. For both rats and mice, significance levels of two tests are provided: 1) a test of trend starting from the vehicle control (Control 1) over the three Lacosamide treatment groups, and 2) a test comparing the vehicle control to the High dose group. The number of tumors in the negative control group is used to determine if the tumor is classified as "rare" or as "common", with the effect on interpretation as outlined below. The Sponsor's report indicates that tests of trend presented also follow the Peto methodology, while Fisher's exact tests were used for pairwise comparisons.

Recent FDA analyses have also used so-called poly-k methods (Bailer & Portier, 1988, and Bieler & Williams, 1993), as well as an apparently new, hierarchical Bayesian approach. However, in this study, actual tumor incidence is too low to justify the effort required for these supporting analyses.

1.3.1.3. Multiplicity of Tests on Neoplasms:

Testing the various neoplasms involved a large number of statistical tests, which in turn necessitated an adjustment in experiment-wise Type I error. Current FDA practice is based on the Haseman-Lin-Rahman rules. Namely, based on his extensive experience with such analyses, for pairwise tests comparing control to the highest dose group, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. For a standard chronic study in two species, i.e., rats and mice, based on simulations and their experience, Lin & Rahman (1998) proposed a further p-value adjustment for tests of trend. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors should be tested at a 0.025 (2.5%) level and common tumors at a 0.005 (0.5%) level. In this analysis the observed incidence in the negative control was used to decide if a tumor was rare or common (i.e., incidence = 0 or ≥1 in the negative control group). This approach was intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation).

1.3.1.4. Validity of the Designs:

When determining the validity of designs there are two key points:
1) adequate drug exposure
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that a survival rate of about 25 animals, out of 50 or more animals, between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. Note that this is exceeded in all Lacosamide dose groups, and may suggest that the MTD was not achieved.

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span.' " The values in the following tables are copied from or derived from the Sponsor's reports and give the final weight and the final percent weight change relative to the pooled control in each study. Note that, roughly, this criterion was only slightly exceeded in male rats but seemed to be clearly exceeded in male mice.

Table 3: Relative Weight Change (compared to control)

Study 13295/00: Rats Group number & label	Dose Level (mg/kg/day)	Mean Weight Gain at Study End			
		Males (g)	% from Vehicle	Females (g)	% from Vehicle
1. Negative Control	0 water	388.0		216.0	
2. Vehicle Control	0	376.7		207.5	
3. Low	40	358.8	-4.8%	235.1	13.3%
4. Medium	80	363.1	-3.6%	221.0	6.5%
5. High	160/180/200*	326.1	-13.4%	200.7	-3.3%

* In the High dose group in females dosage was increased to 180 mg/kg/day in week 51 and to 200 mg/kg/day by Week 74.

Study 13124/00: Mice Group number & label	Dose Level (mg/kg/day)	Mean Weight Gain at Study End			
		Males (g)	% from Vehicle	Females (g)	% from Vehicle
1. Negative Control	0 water	10.9		9.1	
2. Vehicle Control	0	10.1		9.5	
3. Low	20	8.7	-13.9%	8.9	-6.3%
4. Medium	60	8.6	-14.9%	8.2	-13.7%
5. High	180	6.0	-40.6%	8.4	-11.6%

The high dose group in male mice was associated with a weight decrement over vehicle controls considerably larger than the 10% bound cited above. This weight differential in the High dose group may be evidence that the MTD was exceeded. Note however that there was no clear impact on mortality in the high dose group (please see Table 11 below or the Kaplan-Meier estimates of survival in Appendix 1.

For another way of investigating the MTD, note again from 2) above, that large excess mortality not associated with any tumor or sacrifice in the higher dose groups could be used to indicate that the MTD was exceeded. Further, lower mortality in the higher dose groups may also suggest that the MTD was not achieved. To this reviewer a natural way to assess this possibility is to measure mortality not associated with any identified tumor. Note this seems to be a new way to assess if the high dose is at the MTD and needs to be evaluated. Table 4 below indicates the number of animals in each dose group that died of a natural death or moribund sacrifice, but did not show any tumors:

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Table 4: Natural Death or Accident with No Identified Tumor

Rats Group Label	Dose mg/kg	Males		Females	
		Died w/o tumor	Other	Died w/o tumor	Other
1. Negative Control	0 water	7	43	5	45
2. Vehicle Control	0	8	42	5	45
3. Low	40	9	41	8	42
4. Medium	80	7	43	4	46
5. High	160	8	42	5	45

Mice Group Label	Dose Mg/kg	Males		Females	
		Died w/o tumor	Other	Died w/o tumor	Other
1. Negative Control	0 water	11	39	10	40
2. Vehicle Control	0	7	43	11	39
3. Low	20	8	42	19	31
4. Medium	60	7	43	14	36
5. High	180	11	39	14	36

To compare the incidence of deaths without tumors we can specify the usual survival tests where animals' death without a tumor is the event and those animals that die with a tumor or are sacrificed are considered as censored, i.e. they are in the risk set until they die or are sacrificed. Thus the events correspond to animals that die prior to developing a tumor. If the MTD is exceeded, we would expect a dose related excess toxicity, resulting in higher events in the higher dose group or possibly even a dose related trend in these events. The null hypothesis of homogeneity over dose groups in the occurrence of events can be tested with the usual log-rank or Wilcoxon tests. The results of these tests are summarized in Table 5 below:

Table 5: Statistical Significances of Tests of Homogeneity in Death With No Tumor

	Rat Males		Females		Mice Males		Females	
	LogRnk	Wilcox	LogRnk	Wilcox	LogRnk	Wilcox	LogRnk	Wilcox
Homogeneity over all	0.5827	0.4209	0.9447	0.8695	0.9704	0.9433	0.1367	0.1215
Homogeneity over Lac groups	0.5089	0.3374	0.2983	0.7077	0.9146	0.8721	0.1639	0.1715

In both species, in both genders, there was no clear evidence of heterogeneity in these events (all log-rank p and Wilcoxon $p \geq 0.1215$). The observed p-values were about what one would expect with absolutely no effect due to treatment. However, the slightly lower or equal incidence of events in the High dose group in both male and female rats, as well as female mice, might be interpreted as evidence that the MTD was not achieved.

The above evaluation of the validity of the study designs was based on body weight and mortality data. The pharm/tox reviewers should use their expertise and other information such as clinical signs or severe histopathologic toxic effects that are attributable to the dosed animals in their final evaluation of the appropriateness of the doses used.

1.3.2. Statistical Findings

Please see Section 1.1 above.

2. INTRODUCTION

2.1. Overview

Results from a study in CD® rats and CD-1 mice were submitted to assess the carcinogenic potential of SPW-927.

2.2. Data Sources

SAS transport files, labeled as sascorr-for-lpt-13295.xpt and sascorr-for-lpt-13124.xpt, for rats and mice, respectively were submitted by the Sponsor and loaded into the agency electronic data room (edr). Note data for one female rat in the High dose group seems to be missing from the provided data set, so this particular treatment group has 49 animals. Using the identification numbers of the other rats this seems to correspond to the rat with ID number 488. The remaining dose groups in both genders in both species each have data for 50 animals. Note that deleting this one animal should have little impact upon conclusions.

The Sponsor's reports lack page numbers, which interferes with easy reference to various parts of the reports. Cited page numbers have been inferred from the respective tables of contents.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

NA

3.2. Evaluation of Safety

More detailed results on the study are presented below.

3.2.1. Study Report 13295/00 104-Week Carcinogenicity Study by SPM 927 by Oral Administration to CD® Rats,

RAT STUDY DURATION: 104 Weeks.
DOSING STARTING DATE: 06 August 2001.
TERMINAL SACRIFICE: 04 August 2003.
EARLY DOSING MODIFICATION: Females: High Dose Group to 180 mg/kg/day Week 51.
                                            High Dose Group to 200 mg/kg/day Week 74.
STUDY ENDING DATE (Final Report dated): April, 2006.
RAT STRAIN: ——————— ... GmBH CD® —' CD®BR.   **b(4)**
ROUTE: Daily Oral gavage (5 mL/kg).

Five treatment groups were formed per gender, each with 50 CD® rats to assess the carcinogenic potential of drug compound SPM 927 (Lacosamide®), administered by daily gavage for two years. These groups were a negative control (tap water), a vehicle control, and 40, 80, and, initially 160 mg/kg/day SPM 927 dose groups. The vehicle was 0.5% aqueous hydroxypropyl-methylcellulose gel. The five dose groups per gender were labeled in the FDA analysis as Control 0, Control 1, Low, Medium, and High dose groups, respectively. The Sponsor's analysis also labels these as dose groups 1 to 5, respectively. As noted below, in female rats, the 160 mg/kg/day dose group was increased to 180 and later to 200 mg/kg/day.

The Sponsor notes: "For this experiment a total of 560 CD (—' CD®BR) rats (without reserve animals) with an almost identical date of birth and within a weight range of 10 g for each sex was ordered from ———————————————— see section 7 'Study plan deviations').   **b(4)**
At initiation of treatment the animals were not older than approx. 6 weeks. Upon arrival, the animals were given a thorough examination. Rats considered unsatisfactory were sacrificed. The animals were weighed and allocated to each of the 5 test groups using a random number table."
(page 35 of report)

Within each gender, in each of the Low, Medium, and High dose groups an additional 10 animals were assigned as satellite animals for toxicokinetic analysis. The satellite animals were treated for only 52 weeks. After blood withdrawal in Week 52 the satellite animals were sacrificed but not dissected.

The Sponsor provides the following rational for dose selection:
"The dosages have been selected based on the findings of 1-month dose range finding and 3-month oral toxicity studies (——————————————— report no. 1108-005, —————   **b(4)**
report no. —' 148-234, ' —— report no. 148-235). Based on these studies, the no-observed adverse-effect-level (NOAEL) was 100 mg/kg b.w./day. 300 mg/kg b.w./day resulted in mortality. On the basis of the severity/incidence of clinical observations at 200 and 300 mg/kg b.w./day, the high dose for the carcinogenicity study should not exceed 200 mg/kg b.w./day.

"After consideration of these data, discussions with the sponsor and on recommendation of the

Carcinogenicity Assessment Committee (CAC), the dose levels of 40, 80 and 160 mg SPM 927/kg b.w./day were chosen for the carcinogenicity study in the rat.

"As the selected initial high dose of 160 mg/kg appeared not to result in a sufficient degree of toxicity in the female animals as required by the ICH guidelines on the dose selection for carcinogenicity studies of pharmaceuticals, on request of the sponsor and in agreement with the CAC of the FDA, the dose level for the high dosed females was increased from 160 to 180 mg/kg b.w./day from test week 51 (22 Jul 2002) onwards and due to subsiding signs of toxicity from test day 516 (test week 74, 03 Jan 2003) onwards from 180 to 200 mg/kg b.w./day." (page 40)

Animals were approximately six weeks old at first dosing. During the study, animals were housed individually. Food and water were available ad libitum. The Sponsor states that animals were monitored several times each day. Body weights were recorded weekly for the first 13 weeks, beginning approximately one week before initiation of dosing, and every two weeks thereafter.

3.2.1.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in rats.

Survival analysis:

The Sponsor's Week 104 summary survival rates and mean survival times are given in the following table:

Table 6: Sponsor's Summary Survival

	Survival Rates [%] in Week 104		Mean Survival Time	
Group	Males	Females	Males	Females
1. Negative Control	58%	60%	93.1	94.0
2. Vehicle Control	64%	68%	98.1	98.0
3. Low	68%	70%	98.7	97.5
4. Medium	74%	58%	97.2	95.1
5. High	58%	54%	90.1	95.5

The Sponsor states that "No test item-related influence was noted on the survival rates of male and female animals treated with either 40, 80, or 160 SPM 927/kg b.w./day (males) or 40, 80, or 160/180/200 SPM 927/kg b.w./day (females) when compared to the vehicle control.

"The mortality rates of the high dosed males appeared to be increased (statistically significant at $p \leq 0.05$ or $p \leq 0.01$) between test weeks 61 and 94, however, no difference was noted in test week 104." (page 65)

Tumorigenicity analysis:

According to the Sponsor: "There was no difference in the type or incidence of the neoplastic lesions diagnosed in the various organs of test-related rats and control animals (negative and vehicle control group).

"No difference was observed between the vehicle and the negative control.

"The total number of primary neoplasms, animals with neoplasms, rats with more than one primary neoplasm, and animals with metastases were similar in the test item-treated animals, the vehicle control and the negative control rats." (page 95)

3.2.1.2 FDA Reviewer's Results

This section will present the current Agency findings on survival and tumorigenicity in male and female mice.

Survival analysis:

The following tables (Table 7 for male mice, Table 8 for female mice) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived at the end of the interval.

Table 7: Summary of Male Rat Survival (dose/kg/day)

Period (Weeks)	Negative Control 0	Vehicle Control 1	Low 40 mg	Medium 80 mg	High 160 mg
0-50	3/50[1] 94%[2]	1/50 98%	1/50 98%	3/50 94%	4/50 92%
51-78	5/47 84%	5/49 88%	2/49 94%	2/47 90%	11/35 70%
79-91	8/42 68%	3/44 82%	6/47 82%	5/45 80%	2/35 66%
92-104	5/34 58%	9/41 64%	7/41 68%	3/40 74%	4/33 58%
Terminal 105	29	32	34	37	29

[1] number deaths / number at risk
[2] per cent survival to end of period.

Table 8: Summary of Female Rat Survival (dose/kg/day)

Period (Weeks)	Negative Control 0	Vehicle Control 1	Low 40 mg	Medium 80 mg	High 160 mg[3]
0-50	3/50[1] 94%[2]	1/50 98%	1/50 98%	1/50 98%	2/49 95.9%
51-78	5/47 84%	4/49 90%	6/49 86%	7/49 84%	5/47 85.7%
79-91	4/42 76%	5/45 80%	3/43 80%	7/42 70%	3/42 79.6%
92-104	8/38 60%	6/40 68%	5/40 70%	6/35 58%	13/39 53.1%
Terminal 105	30	34	35	29	26

[1] number of deaths / number at risk
[2] per cent survival to end of period.
[3] dose increases to 180 mg, then 200 mg

Note that the proportions given above for the High dose group in female rats differ slightly from those cited by the Sponsor in Table 6 above. Apparently this is due to the absence of rat with ID number 488 in the data set provided by the Sponsor.

The statistical significances of the tests of differences in survival across treatment groups are given in Table 9 below. The test for homogeneity is a test that survival is equal across treatment groups, while the test of trend is a test of dose related trend. The Cox test is usually called the logrank test, while the K-W, i.e., Kruskal-Wallis test, is more commonly called the Wilcoxon test or the generalized Wilcoxon test. Note that the Wilcoxon test places more weight on earlier events than does the logrank test.

Table 9: Statistical Significances of Tests of Homogeneity and Trend in Survival

	Rat Males		Females	
	Cox	K-W	Cox	K-W
Homogeneity over all five groups	0.3054	0.2245	0.4413	0.4996
Homogeneity over Lacosamide groups	0.2962	0.2205	0.2983	0.3546
Trend over Lacosamide groups	0.2856	0.1612	0.0866	0.1121
Departure from trend	0.2786	0.2943	0.6898	0.6955

For both genders the hypotheses of homogeneity in survival over the five treatment groups was never rejected at the usual 0.05 level (all four $p \geq 0.2245$). Results were similar when testing homogeneity over the four Lacosamide treatment groups (including the vehicle group) (all four $p \geq 0.2205$). From the Kaplan-Meier plots in Appendix 1 one can see that in females the mortality curves were often somewhat separated but did cross at several time points, consistent with these observations. There was no strong evidence of a trend over the four Lacosamide dose groups (including the vehicle group) (ignoring the negative Control 0),

although the significance level of the Cox test in females was close (Cox p=0.0866). Again, this seems to be consistent with the Kaplan-Meier curves in figure A.1.2 in Appendix 1. Absence of proof is not proof of absence, but these results do seem to be consistent with no strong dose related heterogeneity in mortality.

Tumorigenicity analysis:

Table 10 below shows the potentially significant results in rats. Based on the incidence in the negative control (water only) group, these would be classified as common tumors. Adjusting for multiplicity using the Haseman-Lin-Rahman rules above, the tests of trend in tumor hair follicles and Leydig cell bilateral adenoma were not statistically significant (since p=0.0430 and p=0.0503 > 0.005). Interestingly, in many studies one would use the vehicle control to assess baseline incidence. In that case, each of the tumors listed in the table below would be classified as rare tumors. However, even if classified as rare tumors, in male rats neither of the two tests of trend would be considered to be statistically significant. In female rats, unilateral C cell carcinoma was also not statistically significant (since p = 0.0182 > 0.005). In this case, however if the tumor was classified as rare, the tumor would be classified as statistically significant.

Table 10: Potentially Statistically Significant Tumorgenicity Results

| | Incidence: | | | | | p-values: | |
	Ctr0	Ctrl	Low	Med	High	Trend	Hi vs Ctrl
Male Rats							
Lesion (skin back)							
TUMOUR HAIR FOLLICLE	1	0	0	0	2	0.0430	0.1992
Testicle							
ADENOMA LEYDIG CELL bilat	3	0	0	2	2	0.0503	0.2096
Female Rats							
Thyroids							
C CELL CARCINOMA unilat	1	0	0	0	3	0.0182	0.1324

Complete incidence tables are provided in Appendix 3.

3.2.2. Study Report 13124/00 104-Week Carcinogenicity Study by SPM 927 by Oral Administration to CD-1 Mice,

MOUSE STUDY DURATION: Week 104.
DOSING STARTING DATE: 24 July 2001.
TERMINAL SACRIFICE: Final necropsies: 24 July 2003.
STUDY ENDING DATE (Final Report dated): April 13, 2006.
MOUSE STRAIN: ───────────── ₁CD-1 / ─CD®-1(ICR)BR.   b(4)
ROUTE: Daily Oral Gavage (10 mL/kg).

Structurally almost identical to the rat study described above, five treatment groups were formed per gender, each with 50 CD-1 mice to assess the carcinogenic potential of drug compound SPM 927 (Lacosamide®), administered by daily gavage for two years. These groups were a negative control (tap water), a vehicle control, and 20, 60, and 180 mg/kg/day SPM 927 dose groups. The vehicle was 0.5% aqueous hydroxypropyl-methylcellulose gel. The five dose groups per gender were labeled in the FDA analysis as Control 0, Control 1, Low, Medium, and High dose groups, respectively. The Sponsor's analyses label these as dose groups 1 through 5, respectively.

The Sponsor states that: "For this experiment a total of 590 CD-1 mice (without reserve animals) with an almost identical date of birth and within a weight range which did not exceed 10% of the mean weight for each sex at the time of selection was ordered from ——— ————————— At initiation of treatment the animals were not older than 6 weeks. Upon arrival, the animals were given a thorough examination. Mice considered unsatisfactory were sacrificed. The animals were weighed and allocated to each of the 5 test groups using a random number table." (page 31 of report)

b(4)

The Sponsor provides the following rationale for dose selection:
"The dosages have been selected based on the results of a 13-week dose-range-finding study by oral administration of 0 (vehicle), 30, 60, 120 and 180 mg SPM 927/kg b.w./day to CD-1 mice ——ᴧ Study No. 13123/00). In this study, the no-observed-effect-level (NOEL) was 30 mg/kg b.w./day." (page 36 of report)   The Sponsor notes that a number of toxicological signs and symptoms were observed at the higher doses, with increasing frequency over dose. Plus, a "comparison of mouse C_{max} at 120 mg SPM 927/kg b.w. with human C_{max} at 300 mg SPM 927 twice daily resulted in a C_{max} ratio of approx. 3. After consideration of these data, discussions with the sponsor and on recommendation of the Carcinogenicity Assessment Committee (CAC), the dose levels of 20, 60 and 180 mg SPM 927/kg b.w./day were chosen for the carcinogenicity study in the mouse. (page 36 of report)

b(4)

Animals were approximately six weeks old at first dosing. During the study, animals were housed individually. Food and water were available ad libitum. Body weights were recorded weekly for the first 13 weeks, beginning approximately one week before initiation of dosing, and every two weeks thereafter.

3.2.2.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in mice.

Survival analysis:
The Sponsor's Week 104 summary survival rates and mean survival times are given in the following table (Table 11):

Table 11: Sponsor's Summary Survival

	Survival Rates [%] in Week 104		Mean Survival Time	
Group	Males	Females	Males	Females
1. Negative Control	38%	44%	91.6	87.3
2. Vehicle Control	46%	40%	94.0	92.0
3. Low	46%	68%**	92.0	96.5
4. Medium	34%	50%	91.1	93.4
5. Low	44%	52%	89.4	89.0

** significantly different from the vehicle control at $p \leq 0.01$ (Fisher Exact Test)

Tumorigenicity analysis:

The Sponsor provides conclusions that are very similar to the results in the rat study, i.e.: "There was no difference in the type or incidence of the neoplastic lesions diagnosed in the various organs of test-related mice and control animals (negative and vehicle control group).

"No difference was observed between the vehicle and the negative control.

"The total number of primary neoplasms, animals with neoplasms, mice with more than one primary neoplasm, and animals with metastases were in all organs similar in the test item-treated, negative and vehicle control group, or slightly decreased in the high dose animals (group 5)." (page 85)

3.2.2.2 FDA Reviewer's Results

This section will present the current Agency findings on survival and tumorigenicity in male and female mice.

Survival analysis:

Again, Kaplan-Meier plots comparing survival among treatment groups in both studies are given in Appendix 1, along with more details of the analysis. The following tables (Table 12 for male rats, Table 13 for female rats) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived to the end of the interval.

Table 12: Summary of Male Mice Survival (dose/kg/day)

Period (Weeks)	Negative Control 0	Vehicle Control 1	Low 20 mg	Medium 60 mg	High 180 mg
0-50	0/50[1] 100%[2]	0/50 100%	3/50 94%	0/50 100%	3/50 94%
51-78	10/50 80%	10/50 80%	6/47 82%	11/50 78%	11/47 72%
79-91	14/40 52%	7/40 66%	13/41 56%	8/39 62%	6/36 60%
92-104	7/26 38%	10/33 46%	5/28 46%	14/31 34%	8/30 44%
Terminal 105	19	23	23	17	22

[1] number deaths / number at risk
[2] per cent survival to end of period.

Table 13: Summary of Female Mice Survival (dose/kg/day)

Period (Weeks)	Negative Control 0	Vehicle Control 1	Low 20 mg	Medium 60 mg	High 180 mg
0-50	4/50[1] 94%[2]	1/50 98%	3/50 94%	1/50 98%	4/50 92%
51-78	12/46 68%	13/49 72%	5/47 84%	10/49 78%	10/46 72%
79-91	6/34 56%	5/36 62%	2/42 80%	7/39 64%	2/36 68%
92-104	6/28 44%	11/31 40%	6/40 68%	7/32 50%	8/34 52%
Terminal 105	22	20	34	25	26

[1] number deaths / number at risk
[2] per cent survival to end of period.

The statistical significances of the tests of differences in survival across treatment groups are given in Table 14 below. The test for homogeneity is a test that survival is equal across treatment groups, while the test of trend is a test of dose related trend. The Cox test is usually called the logrank test, while the K-W, i.e., Kruskal-Wallis test, is more commonly called the Wilcoxon test or the generalized Wilcoxon test. Note that the Wilcoxon test places more weight on earlier events than does the logrank test.

Table 14: Statistical Significances of Tests of Homogeneity and Trend in Survival

	Mice Males		Females	
	Cox	K-W	Cox	K-W
Homogeneity over all	0.8053	0.8509	0.0845	0.1028
Homogeneity over Lacosamide groups	0.7031	0.7385	0.0772	0.1205
Trend over Lacosamide groups	0.6782	0.4416	0.8517	0.6303
Departure from trend	0.5384	0.7159	0.0333	0.0610

For both species and genders the hypotheses of homogeneity in survival over the five treatment groups was never rejected at the usual 0.05 level (all eight $p \geq 0.0772$), though results were close to significance in female mice. However, when attention is restricted to the testing homogeneity over the four Lacosamide treatment groups (including the vehicle group) no results were even close to statistical significance (all four $p \geq 0.4416$). The only statistically significant test in the table is the test of departure from linear trend in female mice (Cox $p=0.0333$). This seems to be consistent with the Kaplan-Meier curves in figure A.1.4 in Appendix 1. Absence of proof is not proof of absence, but these results do seem to be consistent with no strong dose related heterogeneity in mortality.

Tumorigenicity analysis:

Tables A.3.4 and A.3.5 in Appendix 3 indicate tumor incidence in the mice data set provided by the Sponsor. No tests of trend or pairwise differences between the High dose group and the vehicle controls were even nominally statistically significant at the 0.05 level, let alone after adjusting for multiplicity using the Haseman-Lin-Rahman rules described Section 1.3.1.3 above.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

NA

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

5.2. Conclusions and Recommendations

Please see section 1.1 above.

APPENDICES:

Appendix 1. Survival Analysis

The statistical significances of the tests of differences in survival across treatment groups are given in Table A.1 below. The test for homogeneity is a test that survival is equal across treatment groups, while the test of trend is a test of dose related trend. The Cox test is usually called the logrank test, while the K-W, i.e., Kruskal-Wallis test, is more commonly called the Wilcoxon test or the generalized Wilcoxon test. Note that the Wilcoxon test places more weight on earlier events than does the logrank test. The test for homogeneity "over all" tests for differences in mortality among the five treatment groups, i.e. the negative control, the vehicle control, and the three Lacosamide treatment groups. The tests over the "Lac" groups are tests over the vehicle control and the three Lacosamide treatment groups.

Table A.1. Statistical Significances of Tests of Homogeneity and Trend in Survival

	Rat Males		Females		Mice Males		Females	
	Cox	K-W	Cox	K-W	Cox	K-W	Cox	K-W
Homogeneity over all five groups	0.3054	0.2245	0.4413	0.4996	0.8053	0.8509	0.0845	0.1028
Homogeneity over four Lacosamide groups	0.2962	0.2205	0.2983	0.3546	0.7031	0.7385	0.0772	0.1205
Trend over Lac. groups	0.2856	0.1612	0.0866	0.1121	0.6782	0.4416	0.8517	0.6303
Departure from trend	0.2786	0.2943	0.6898	0.6955	0.5384	0.7159	0.0333	0.0610

For both species and genders the hypotheses of homogeneity in survival over the five treatment groups is never rejected at the usual 0.05 level (all eight $p \geq 0.0845$), though results are close to significance in female mice. Results are similar when testing homogeneity over the four Lacosamide treatment groups (including the vehicle group) (all eight $p \geq 0.0772$), although again results are fairly close to statistical significance in the Cox test in female mice. From the Kaplan-Meier plot in Figure A.1.4 below one can see that in female mice the mortality curves are often somewhat separated but repeatedly cross, consistent with these observations. There is no strong evidence of a trend over Lacosamide dose groups (ignoring the negative Control 0), although the Cox test in female rats is close (Cox p=0.0866). Again this seems to be consistent with the Kaplan-Meier curves in figure A.1.2 below. The only statistically significant test in the table is the test of departure from linear trend in female mice (Cox p=0.0333). This seems to be consistent with the Kaplan-Meier curves in figure A.1.4 below. Absence of proof is not proof of absence, but these results do seem to be consistent with no strong dose related heterogeneity in mortality.

The figures below display these Kaplan-Meier estimated survival curves for the two genders in each rodent species.

Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats
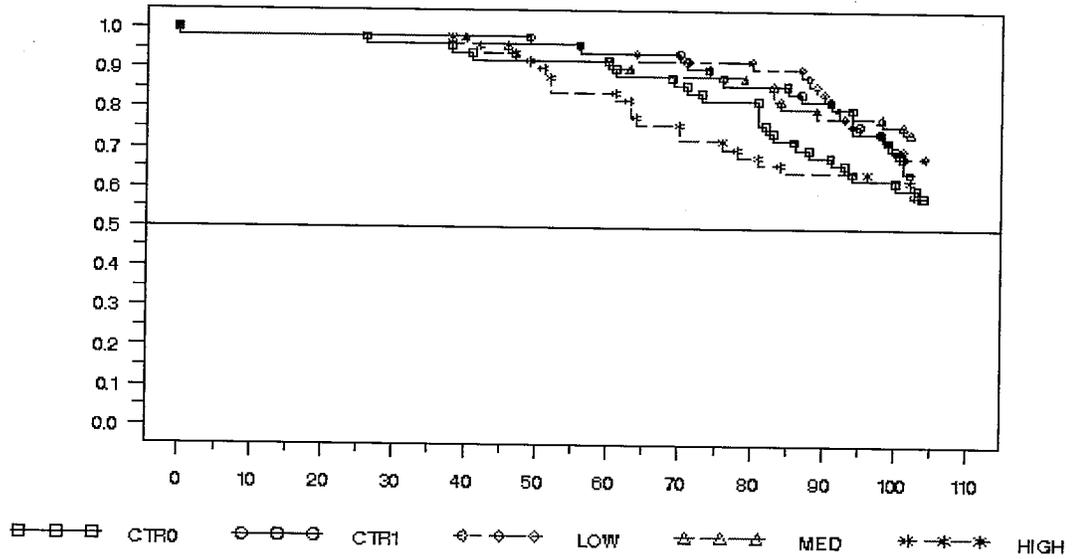
For female mice the survival plots intertwine as depicted below:

Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats
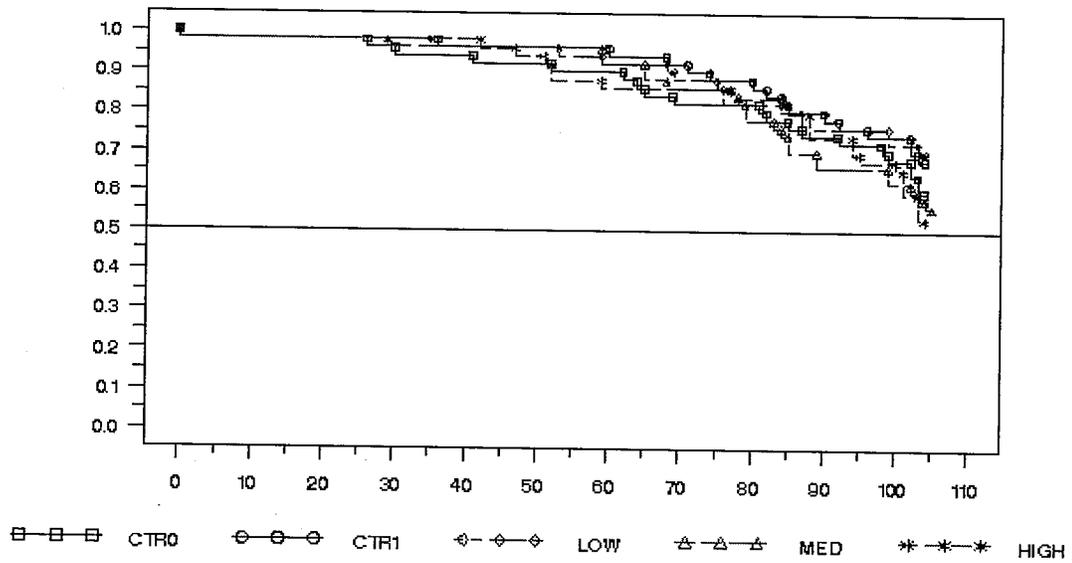
Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice
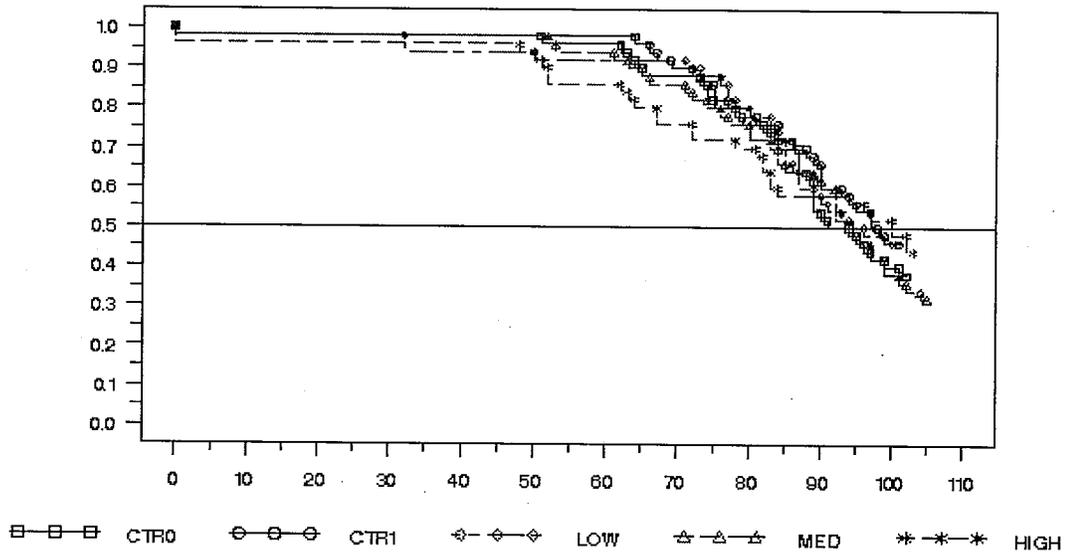
For female mice the survival plots seem somehat more separated, but still repeated cross as depicted below:

Figure A.1.4 Kaplan-Meier Survival Curves for Female Mice
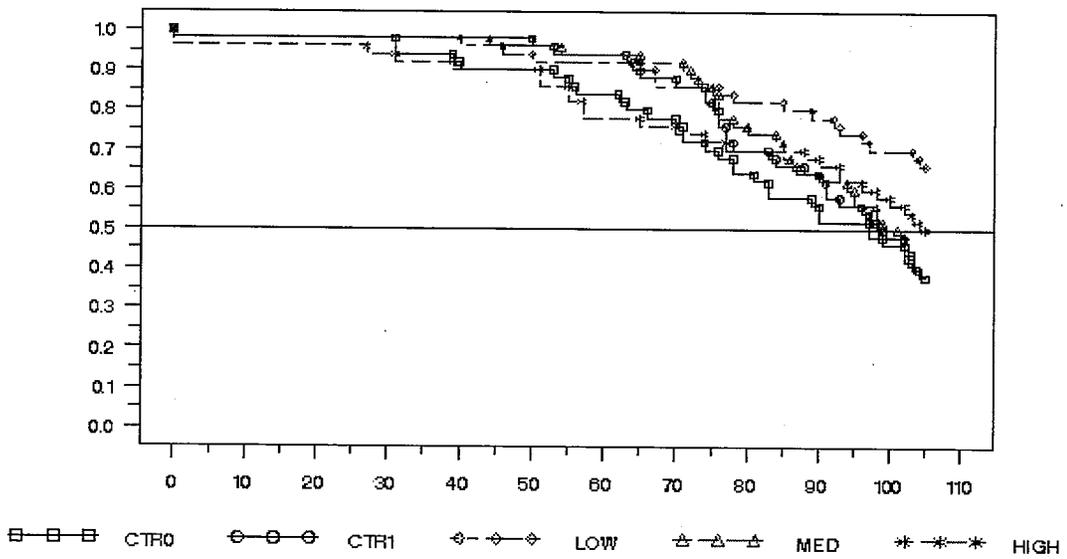
Appendix 2. Bayesian Analysis of Survival

Let $S(t)$ be the survival function, i.e., with T denoting the survival time,
$$S(t) = Pr(T > t),$$
and $f(t)$ the density of T. The instantaneous hazard function is $h(t) = f(t)/S(t)$ with cumulative hazard:

$$H(t_i) = \int_0^{t_i} h(u)du$$

So $f(t) = h(t) S(t)$. Also $log(S(t)) = -H(t)$, so $S(t) = e^{-H(t)}$. Then $f(t) = h(t) e^{-H(t)}$.

The standard Cox regression form of the proportional hazards model for survival specifies the hazard function:
$$h(t \mid x) = h_0(t) \, exp(x'\beta).$$

Frequentist analysis of this model uses asymptotics to analyze the linear predictor, ignoring the baseline hazard $h_0(t)$. A Bayesian analysis requires priors on all parameters, including the baseline hazard. Perhaps the simplest Bayesian model would postulate a within interval constant baseline hazard. For this analysis, the intervals for the constant baseline were chosen as (0,366], (366,500], (500,600], (600,660], and (660, terminal].

Thus we need to specify an appropriate prior for the baseline hazard. Note that the baseline hazard is essentially the hazard of the control group. An unbounded uniform prior on the baseline hazards is improper but, at least in this case, results in a proper posterior distribution, and, partly for experimental reasons, was chosen as the prior for this analysis. The priors on regression parameters were a well dispersed normal distribution (i.e., N(0.0,100,000)).

In each study, over both genders, there were five "treatment" groups, including the negative control and the vehicle control. In the Cox proportional hazards model, the baseline hazard is partially confounded with the specification of treatment effects (i.e., a multiplicative constant can be moved to either the baseline hazard or the term with covariates). So, in this case one always loses one degree of freedom from the number of treatment groups when testing for differences among the treatment groups.

When parameterizing each treatment group separately, using so called dummy coding, we can define, for each treatment group i, except a reference dose:

$\delta_i =$ 1 for the ith treatment group,
         0 otherwise.
With this parameterization each labeled effect actually represents the differential effect of the specified treatment over the effect of the reference dose. Then it would seem to be appropriate to define either the negative control or the vehicle as the reference dose.

At least five possible models are suggested:

Over all the five treatment groups:

(1) Parameterization of no differences in survival across treatment groups with negative control (water) (i.e., constant dose effect) $x_i^t\beta = \beta_0$.

(2) Parameterization of a differential effect of the vehicle and Lacosamide groups over the negative controls, i.e.: $x_i^t\beta = \beta_0 + \beta_1*\delta_1 + \beta_2*\delta_2 + \beta_3*\delta_3 + \beta_4*\delta_4$.

Over the four treatment groups with vehicle:

(3) Parameterization of no differences in survival across treatment groups with the vehicle (i.e., constant dose effect) $x_i^t\beta = \beta_0$.

(4) Parameterization of a differential effect of the Lacosamide groups over the vehicle, i.e.: $x_i^t\beta = \beta_0 + \beta_1*\delta_1 + \beta_2*\delta_2 + \beta_3*\delta_3$.

(5) Parameterization of a linear effect of dose in the Lacosamide groups plus vehicle, $x_i^t\beta = \beta_0 + \beta_1* \text{ dose}$.

Note again, that for each of these models $\exp(\beta_0)$ is confounded with the baseline hazard $h_0(t)$ and is not estimated. In models (2) and (4) above, β_k measures the differences between the kth dose in the model and the reference dose group, either the negative control or the vehicle, respectively. The program used for this analysis was the experimental SAS® procedure, PROC BPHREG. Because this is a new procedure and is still considered to be experimental, this analysis, at best, can only be considered to be supporting.

One possible approach to model selection is to use the so-called information criteria measures. These attempt to assess the information about the parameters in the model. One such measure is the Bayesian Information Criterion (BIC), defined as -2 x the maximized log likelihood – (# of free parameters to be estimated) x log (# of observations). In general, within a specific data set, the model with smallest BIC is considered to be the best among the listed models:

BIC	Rats		Mice	
	Males	Females	Males	Females
With negative control				
Constant effects	1804.6	1931.1	2876.6	2506.6
Heterogeneity in treatments	1817.7	1945.5	2894.7	2517.6
Deleting negative control				
Constant effects	1352.9	1493.7	2232.3	1906.4
Heterogeneity in treatments	1362.0	1502.8	2244.9	1913.0
Trend in dose	1356.0	1495.6	2236.9	1910.9

In general, for model selection in Bayesian models this reviewer would prefer to use the Deviance Information Criterion (DIC). However, the test version SAS BPHREG procedure has a programming error when computing the DICs (personal communication from the SAS technical help). Using the BIC, within each data set, whether with or without the negative controls, among the models above, the models with no dose effects seem to be the best.

Tables A.2.1 and A.2.2, below, summarize the estimated posterior distributions of the treatment group parameters in the rat study and mouse study, respectively. The two right most columns provide the lower and upper endpoints of an estimated 95% credible interval. That is, the posterior probability that the parameter is in the interval is 0.95. One way to translate this to a hypothesis testing framework is to suggest that if 0 is in the posterior interval we would conclude that the parameter could be zero. Note that in the rat study, for both genders, whether we consider all the differences from the negative control or differences from the vehicle control, or simple trend, all intervals include zero, usually relatively distant from a boundary of the interval. This can be interpreted that in rats there is no evidence in mortality differences among the treatment groups, consistent with the results from the BIC.

Table A.2.1 Posterior Summaries of Treatment Parameters in the Rats Study

Parameter	Mean	Standard Deviation	25%	Quantiles 50%	75%	HPD Credible Interval
Male Rats						
Overall Versus Negative Control						
Vehicle	-0.2527	0.3221	-0.4674	-0.2486	-0.0335	-0.8912,0.3656
Low	-0.3899	0.3357	-0.6110	-0.3868	-0.1633	-1.0723,0.2455
Medium	-0.5919	0.3552	-0.8261	-0.5881	-0.3525	-1.2927,0.1094
High	0.0598	0.3103	-0.1494	0.0623	0.2695	-0.5592,0.6529
Lacosamide Versus Vehicle						
Low	-0.1334	0.3502	-0.3681	-0.1267	0.1017	-0.8050,0.5623
Medium	-0.3384	0.3684	-0.5806	-0.3343	-0.0887	-1.0613,0.3891
High	0.3115	0.3258	0.0889	0.3106	0.5325	-0.3194,0.9504
Trend from Vehicle over Lacosamide doses						
Dose	0.0856	0.0828	0.0305	0.0864	0.1413	-0.0754,0.2488
Female Rats						
Overall Versus Negative Control						
Vehicle	-0.2882	0.3415	-0.5166	-0.2878	-0.0582	-0.9602,0.3859
Low	-0.3514	0.3452	-0.5818	-0.3497	-0.1211	-1.0108,0.3433
Medium	0.1103	0.3136	-0.0988	0.1088	0.3198	-0.5065,0.7188
High	0.1690	0.3115	-0.0418	0.1650	0.3767	-0.4411,0.7834
Lacosamide Versus Vehicle						
Low	-0.0650	0.3640	-0.3121	-0.0602	0.1823	-0.7722,0.6526
Medium	0.4002	0.3324	0.1743	0.3964	0.6228	-0.2433,1.0530
High	0.4581	0.3301	0.2345	0.4572	0.6794	-0.1979,1.0909
Trend from Vehicle over Lacosamide doses						
Dose	0.1276	0.0753	0.0771	0.1281	0.1781	-0.0230,0.2716

Table A.2.2, below, provides a similar summary of the estimated posterior distributions of the treatment group parameters in the mouse study. As with rats, all the posterior intervals in male mice include zero, which can be interpreted as no particular evidence of mortality differences among the treatment groups, also consistent with the results from the BIC. However in female mice, neither of the 95% credible intervals for the difference between the low dose group and either control contain zero, thus indicating "significantly" higher mortality in the low dose group than in either control group.

Table A.2.2 Posterior Summaries of Treatment Parameters in the Mice Study

Parameter	Mean	Standard Deviation	25%	Quantiles 50%	75%	HPD Credible Interval
Male Mice						
Overall Versus Negative Control						
Vehicle	-0.2203	0.2628	-0.3940	-0.2186	-0.0448	-0.7460,0.2901
Low	-0.1803	0.2639	-0.3556	-0.1790	-0.00087	-0.7084,0.3252
Medium	0.0924	0.2480	-0.0726	0.0945	0.2598	-0.3881,0.5778
High	-0.1014	0.2609	-0.2741	-0.0994	0.0757	-0.6144,0.4107
Lacosamide Versus Vehicle						
Low	0.0333	0.2734	-0.1490	0.0331	0.2170	-0.5048,0.5719
Medium	0.3072	0.2600	0.1307	0.3048	0.4829	-0.2036,0.8141
High	0.1154	0.2722	-0.0666	0.1135	0.2977	-0.4216,0.6495
Trend from Vehicle over Lacosamide doses						
Dose	0.00976	0.0265	-0.00795	0.0101	0.0278	-0.0407,0.0627
Female Mice						
Overall Versus Negative Control						
Vehicle	0.0274	0.2661	-0.1524	0.0276	0.2060	-0.4968, 0.5405
Low	-0.7495	0.3142	-0.9594	-0.7436	-0.5356	-1.3633,-0.1343
Medium	-0.2334	0.2788	-0.4189	-0.2317	-0.0464	-0.7851, 0.3119
High	-0.2088	0.2817	-0.3967	-0.2080	-0.0204	-0.7730, 0.3310
Lacosamide Versus Vehicle						
Low	-0.7814	0.3069	-0.9834	-0.7756	-0.5734	-1.3763,-0.1723
Medium	-0.2575	0.2730	-0.4409	-0.2560	-0.0737	-0.7765, 0.2890
High	-0.2392	0.2733	-0.4215	-0.2375	-0.0557	-0.7691, 0.2988
Trend from Vehicle over Lacosamide doses						
Dose	0.00353	0.0295	-0.0161	0.00394	0.0235	-0.0539, 0.0619

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Appendix 3. FDA Peto Tumorigenicity Analysis

Tables A.3.1 through A.3.5 below display the number of neoplasms in each organ and tumor combination. Table A.3.1 shows the neoplasms whose mortality adjusted tests were statistically significant or close to significance. Tables A.3.2 and A.3.3 below, show the results for male and female rats, respectively, while tables A.3.4 and A.3.5 present similar results in male and female mice. These values were taken from the SAS datasets provided by the Sponsor. For each dose group, the tumor incidence is the number of animals where histopathological analysis detected a tumor. The Sponsor indicates that for all tumors specified in the protocol, all animals in each treatment group were microscopically examined. The column labled "Trend" provides the observed p-value of the tests of trend over the vehicle controls, and the low, medium, and high dose groups. The column labled "High vs Ctrl" provides the significance levels of the tests comparing the high dose group in each gender by species combination to the vehicle control group. For 10 or fewer tumor bearing animals in the comparison, the reported significance levels came from exact tests (i.e., assuming that the marginal totals for the number of animals with and without the neoplasm are fixed). For more than 10 tumor bearing animals large sample, asymptotic tests were used.

The Haseman-Lin-Rahman rules summarized below are designed to adjust for the multiplicity of tests over the organ by tumor combinations and determine if the observed p-value is statistically significant. That is, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level to the appropriate bound below:

Haseman - Lin - Rahman Bounds: Comparison	Rare Tumor (Incidence ≤ 1%)	Common Tumor (Incidence > 1%)
Trend (over 3 or more groups)	0.025	0.005
Pairwise	0.05	0.01

The tumor incidence in the negative control is used to determine if the tumor is rare (with incidence ≤ 1%, i.e., no tumor), or common (with incidence > 1%, i.e., 1 or more tumors). Thus, for example, in a two species, two gender study, if a tumor is classified as rare, the pairwise test between the high dose group and control would be considered statistically significant at a roughly 10% level if the computed significance level was at or less than 0.05.

No comparisons or trends in either gender in mice were particularly close to statistically significant. Table A.3.1 below shows the potentially significant results in rats. Based on the incidence in the negative control (water only) group, these would be classified as common tumors. Adjusting for multiplicity using the Haseman-Lin-Rahman rules above, the tests of trend in tumor hair follicles and Leydig cell bilateral adenoma were not statistically significant (since p=0.0430 and p=0.0503 > 0.005). Interestingly, in many studies one would use the vehicle control to assess baseline incidence. In that case, each of the tumors listed in Table A.3.1 would be classified as rare tumors. However, even if classified as rare tumors, in male rats

neither of the two tests of trend would be considered to be statistically significant. In female rats, unilateral C cell carcinoma was also not statistically significant (since p = 0.0182 > 0.005). In this case, however if the tumor was classified as rare the tumor would be classified as statistically significant.

Table A.3.1. Potentially Statistically Significant Tumorgenicity Results

	Incidence: Ctr0	Ctr1	Low	Med	High	p-values: Trend	Hi vs Ctr1
Male Rats							
Lesion (skin back)							
TUMOUR HAIR FOLLICLE	1	0	0	0	2	0.0430	0.1992
Testicle							
ADENOMA LEYDIG CELL bilat	3	0	0	2	2	0.0503	0.2096
Female Rats							
Thyroids							
C CELL CARCINOMA unilat	1	0	0	0	3	0.0182	0.1324

Complete incidence tables follow:

Table A.3.2. Tumorgenicity in Male Rats

	Incidence: Ctr0	Ctr1	Low	Med	High	p-values: Trend	Hi vs Ctr1
Adrenals							
CORTICAL ADENOCARCINOMA	0	0	0	0	1	0.2137	0.4630
CORTICAL ADENOMA unilat	1	6	5	0	4	0.7741	0.7285
Cortical Adenoma/-carcinoma	1	6	5	0	5	0.6145	0.4917
HAEMANGIOMA	0	0	0	0	1	0.2137	0.4630
PHAEOCHROMOCYTOMA	0	2	2	5	2	0.3393	0.5312
PHAEOCHROMOCYTOMA malignant	0	0	1	1	0	0.6024	
Brain (cerebellum)							
HAEMANGIOMA	1	0	0	0	0		
Brain (cerebrum)							
ASTROCYTOMA benign	1	1	1	0	0	0.8909	1.0000
ASTROCYTOMA malignant	1	0	0	0	0		
GRANULAR CELL TUMOUR	0	1	0	0	0	1.0000	1.0000
MEDULLOBLASTOMA	0	1	0	0	1	0.4690	0.7203
MIXED GLIOMA	0	1	1	0	1	0.6870	0.8227
Brain stem							
ASTROCYTOMA	0	0	0	1	0	0.5263	
Haematopoietic system							
LARGE GRANULAR LYMPH LEUCAE	2	0	0	0	0		
LYMPHOMA LYMPHOBLASTIC TYP	0	0	0	0	1	0.2137	0.4630
LYMPHOMA PLEOMORPHIC TYPE	2	0	1	0	0	0.7351	
Heart							
ENDOCARDIAL SCHWANNOMA BENI	0	0	0	0	1	0.2137	0.4630
MESOTHELIOMA ATRIOCAVAL MAL	0	1	0	0	0	1.0000	1.0000
Kidneys							
RENAL LIPOSARCOMA	0	0	0	1	0	0.4872	
RENAL MESENCHYM TUMOUR mali	0	0	0	1	0	0.4872	

Table A.3.2. (cont.) Tumorgenicity in Male Rats

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Lesion (axilla)							
FIBROADENOMA mamma	0	0	0	0	1	0.2069	0.4286
Lesion (back region)							
TUMOUR HAIR FOLLICLE	0	0	0	0	1	0.2012	0.4304
Lesion (cranial cavity)							
HAEMANGIOSARCOMA	1	0	0	0	0		
Lesion (ear)							
KERATOACANTHOMA	0	0	0	0	1	0.1847	0.4085
SCHWANNOMA BENIGN	0	0	0	1	0	0.4731	
Lesion (eye lid)							
HAEMANGIOMA	0	0	0	1	0	0.4483	
Lesion (flank)							
FIBROMA	0	0	0	1	0	0.4467	
FIBROSARCOMA	0	1	0	0	0	1.0000	1.0000
TUMOUR HAIR FOLLICLE	0	0	1	0	0	0.7583	
Lesion (fore leg)							
MALIG FIBROC HISTIOCYTOMA	1	0	0	0	0		
Lesion (genital area)							
TRICHOEPITHELIOM	0	0	0	0	1	0.2381	0.4787
Lesion (head neck)							
LIPOMA	0	0	1	0	0	0.7391	
Lesion (head)							
SQUAMOUS CELL CARCINOMA	0	1	0	0	1	0.3957	0.7121
Lesion (lymph node)							
HAEMANGIOSARCOMA	0	1	0	0	0	1.0000	1.0000
Lesion (neck)							
FIBROMA	0	0	0	1	0	0.4833	
Lesion (shoulder)							
BEN FIBRO HISTIOCYTOMA	0	0	0	1	0	0.4601	
FIBROMA MYXOMATOUS	0	0	1	0	0	0.7273	
Lesion (skin back flank)							
FIBROMA	2	0	0	0	0		
Lesion (skin back region)							
HAEMANGIOSARCOMA	0	0	1	0	0	0.7363	
Lesion (skin back)							
TUMOUR HAIR FOLLICLE	1	0	0	0	2	0.0430	0.1992
Lesion (skin flank)							
BEN FIBRO HISTIOCYTOMA	0	0	0	0	1	0.2449	0.4898
Lesion (skin hind leg)							
FIBROMA	0	1	0	0	1	0.4424	0.6864
LIPOMA	0	0	1	0	0	0.7521	
TUMOUR HAIR FOLLICLE	0	1	0	0	0	1.0000	1.0000
Lesion (skin tail)							
FIBROSARCOMA	0	0	0	1	0	0.4483	
Liver							
CARCINOMA NOS	0	0	0	0	1	0.2137	0.4630
HAEMANGIOSARCOMA	0	1	0	0	0	1.0000	1.0000
HEPATOCELLULAR ADENOMA	0	0	2	0	0	0.7579	
HEPATOCELLULAR CARCINOMA	0	1	0	4	1	0.3229	0.7163
Hepat. Adenoma/-carcinoma	0	1	2	4	1	0.4011	0.7163

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Table A.3.2. (cont.) Tumorgenicity in Male Rats

	Incidence: Ctr0	Ctr1	Low	Med	High	p-values: Trend	Hi vs Ctr1
Lungs with bronchi							
ADENOMA BRONCHIOLO ALVEOLAR	0	0	0	1	0	0.4872	
NON-KERATIN SQUAMO C CARCIN	1	0	0	0	0		
SQUAMOUS CELL CARCINOMA	0	1	0	0	0	1.0000	1.0000
Lymph node (mesenteric)							
HAEMANGIOMA	3	1	1	1	2	0.1701	0.3182
HAEMANGIOSARCOMA	1	0	4	3	0	0.7130	
Mammary gland							
FIBROMA	1	1	1	0	0	0.9221	1.0000
Fibroma/-adenoma/-carcinoma	1	1	1	0	0	0.9221	1.0000
MALIG FIBROC HISTIOCYTOMA	0	0	0	0	1	0.2045	0.4426
SARCOMA NOS	0	0	0	1	0	0.4842	
Mononuclear phagocytic tissue							
HISTIOCYTIC SARCOMA	3	1	1	0	2	0.2211	0.4100
Nasal cavity with nasopharynx							
HAEMANGIOMA	0	1	0	0	0	1.0000	1.0000
ODONTOMA	0	0	1	0	0	0.7521	
Pancreas							
ADENOMA ACINAR CELL	0	2	3	3	0	0.8995	1.0000
ADENOMA ISLET CELL	3	2	2	6	4	0.0869	0.1961
Adenoma/-carcinoma Islet Cell	4	2	2	6	4	0.0869	0.1961
CARCINOMA ISLET CELL	1	0	0	0	0		
Parathyroids							
ADENOMA	1	1	2	1	0	0.8114	1.0000
Pituitary							
ADENOCARCINOMA PARS DISTALIS	0	1	3	0	0	0.8952	1.0000
ADENOMA PARS DISTALIS	18	18	19	15	8	0.9735	0.9654
Adenoma/-carcinoma Pars Dist.	18	19	22	15	8	0.9881	0.9766
Preputial gland							
ADENOMA	1	0	0	0	0		
Prostate							
ADENOMA	0	0	1	0	0	0.7521	
Salivary glands							
SCHWANNOMA	0	0	0	1	0	0.5263	
Skin (left flank)							
TUMOUR HAIR FOLLICLE	1	0	0	0	0		
Spinal cord (3 sections)							
ASTROCYTOMA benign	0	1	0	0	0	1.0000	1.0000
Systemic							
Hemangioma	4	2	1	2	3	0.1407	0.3495
Hemangioma/-sarcoma	4	4	6	5	3	0.5729	0.5828
Hemangisarcoma	2	2	5	3	0	0.9019	1.0000
Testicle							
ADENOMA LEYDIG CELL bilat	3	0	0	2	2	0.0503	0.2096
ADENOMA LEYDIG CELL unilat	3	4	4	7	4	0.4265	0.6331
MESOTHELIOMA MALIGNANT	0	0	0	0	1	0.2137	0.4630
Thymus							
THYMOMA	0	1	2	1	1	0.6813	0.8291

Table A.3.2. (cont.) Tumorgenicity in Male Rats

	Incidence:					p-values:	
	Ctr0	Ctrl	Low	Med	High	Trend	Hi vs Ctrl
Thyroids							
ADENOMA C CELL bilat	0	0	1	0	1	0.2763	0.4630
ADENOMA C CELL unilat	2	3	1	0	2	0.6566	0.7747
ADENOMA FOLLICUL CELL bilat	0	0	1	0	0	0.5600	
ADENOMA FOLLICUL CELL unil	2	2	1	1	1	0.7082	0.8527
CARCINOMA FOLLICUL CELL uni	1	1	0	0	2	0.1626	0.4435
Urinary bladder							
TRANSITIONAL CELL PAPILLOMA	0	0	0	1	0	0.2400	
Zymbal glands							
SCHWANNOMA TYPE A	1	0	0	0	0		

Table A.3.3. Tumorgenicity in Female Rats

	Incidence:					p-values:	
	Ctr0	Ctrl	Low	Med	High	Trend	Hi vs Ctrl
Adrenals							
CORTICAL ADENOCARCINOMA	0	1	1	0	0	0.9375	1.0000
CORTICAL ADENOMA bilat	1	0	0	0	0		
CORTICAL ADENOMA unilat	6	6	5	4	3	0.8812	0.9104
Cortical Adenoma/-carcinoma	7	7	6	4	3	0.9402	0.9549
GANGLIONEUROMA MEDULLARY TU	0	1	0	0	0	1.0000	1.0000
PHAEOCHROMOCYTOMA	0	1	0	0	1	0.5407	0.7805
PHAEOCHROMOCYTOMA malignant	1	0	0	0	0		
Brain (cerebellum)							
ASTROCYTOMA malignant	0	1	0	0	0	1.0000	1.0000
Brain (cerebrum)							
ASTROCYTOMA malignant	0	0	1	0	0	0.7515	
GRANULAR CELL TUMOUR	1	0	0	0	0		
MIXED GLIOMA	0	0	1	0	0	0.7560	
OLIGODENDROGLIOMA	0	0	1	0	0	0.7500	
Eyes with optic nerve							
RETINOBLASTOMA	0	0	1	0	0	0.7500	
Haematopoietic system							
LARGE GRANULAR LYMPH LEUCAE	0	1	0	1	1	0.4455	0.7556
LYMPHOMA PLEOMORPHIC TYPE	1	0	0	0	0		
Harderian glands							
HAEMANGIOSARCOMA	0	0	0	1	0	0.4881	
Heart							
ENDOCARDIAL SCHWANNOMA BENI	1	0	0	0	0		
Ileum							
LEIOMYOMA	0	0	0	0	1	0.2381	0.4878
Jejunum							
LEIOMYOMA	0	0	1	0	0	0.7500	
Kidneys							
RENAL LIPOSARCOMA	1	0	0	0	0		
RENAL MESENCHYM TUMOUR mali	0	0	0	0	1	0.2381	0.4878
Lacrimal glands							
ADENOMA unilat	0	1	0	0	0	1.0000	1.0000

Table A.3.3. (cont.) Tumorgenicity in Female Rats

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Lesion (abdominal cavity)							
SCHWANNOMA MALIGN	0	0	0	1	0	0.4286	
SQUAMOUS CELL CARCINOMA	0	0	0	1	0	0.4828	
Lesion (abdominal region)							
LIPOSARCOMA	1	0	0	0	0		
Lesion (anus)							
FIBROADENOMA mamma	0	0	1	0	0	0.7500	
Lesion (axilla)							
ADENOCARCINOMA	0	0	1	0	0	0.7479	
ADENOCARCINOMA mamma	1	0	0	0	0		
ADENOCARCINOMA met	0	2	1	0	0	0.9821	1.0000
FIBROADENOMA mamma	2	2	3	2	0	0.9304	1.0000
FIBROMA	0	0	0	0	1	0.2689	0.5161
Lesion (ear)							
CHONDROSARCOMA	0	1	0	0	0	1.0000	1.0000
Lesion (flank)							
ADENOCARCINOMA mamma	2	0	0	0	0		
FIBROADENOMA mamma	1	1	0	0	0	1.0000	1.0000
Lesion (genital area)							
ADENOCARCINOMA	1	1	0	0	0	1.0000	1.0000
FIBROADENOMA	0	2	0	0	0	1.0000	1.0000
FIBROADENOMA mamma	0	1	1	0	0	0.9335	1.0000
POLYP ENDOMETRIAL STROMAL	0	0	1	0	0	0.7481	
Lesion (head)							
FIBROMA	0	0	0	1	0	0.4828	
SQUAMOUS CELL CARCINOMA	0	1	0	0	0	1.0000	1.0000
Lesion (hind leg)							
ADENOMA mamma	0	0	1	0	0	0.7357	
FIBROADENOMA	0	1	0	1	0	0.8004	1.0000
HAEMANGIOPERICYTOM	0	0	0	1	0	0.4921	
HAEMANGIOSARCOMA	0	0	1	0	0	0.7500	
Lesion (neck)							
BASALIOMA	0	0	1	0	0	0.7453	
FIBROADENOMA mamma	2	1	0	0	0	1.0000	1.0000
FIBROSARCOMA	0	0	0	0	1	0.2368	0.4839
Lesion (right mamma)							
FIBROADENOMA	0	0	1	0	0	0.7500	
Lesion (shoulder)							
OSTEOSARCOMA	0	0	0	1	0	0.5000	
Lesion (skin axilla)							
FIBROADENOMA mamma	0	0	0	0	1	0.2454	0.5000
Lesion (skin hind leg)							
ADENOCARCINOMA mamma	0	0	0	0	1	0.2647	0.5143
FIBROADENOMA mamma	0	0	0	0	1	0.2689	0.5161
Lesion (skin shoulder)							
FIBROADENOMA mamma	0	0	0	0	1	0.3333	0.5714
Liver							
HAEMANGIOSARCOMA	0	1	0	0	0	1.0000	1.0000
HEPATOCELLULAR ADENOMA	0	0	1	0	0	0.7500	
Hepat. Adenoma/-carcinoma	0	0	1	0	0	0.7500	

Table A.3.3. (cont.) Tumorgenicity in Female Rats

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Lungs with bronchi							
HAEMANGIOSARCOMA	0	0	0	0	1	0.2381	0.4878
OSTEOSARCOMA	0	0	0	0	1	0.2650	0.5082
Lymph node (cervical)							
HAEMANGIOMA	0	1	1	0	1	0.6151	0.7805
Lymph node (mesenteric)							
HAEMANGIOMA	0	0	0	1	0	0.4881	
HAEMANGIOSARCOMA	1	0	0	0	0		
Mammary gland							
ADENOCARCINOMA	4	2	4	1	1	0.8515	0.8754
ADENOMA	3	2	5	0	2	0.7515	0.6991
ADENOMA CYSTIC	1	0	0	0	0		
Adenoma/Adenocarcinoma	6	4	7	1	3	0.8408	0.7878
CARCINOMA arising in FIBROA	0	1	1	1	0	0.8428	1.0000
FIBROADENOMA	6	6	9	11	10	0.1970	0.2084
FIBROMA	0	0	1	0	0	0.7500	
Fibroma/-adenoma/-carcinoma	6	7	10	12	10	0.2857	0.2973
Mononuclear phagocytic tissue							
HISTIOCYTIC SARCOMA	1	4	0	0	0	1.0000	1.0000
Ovaries							
GRANULOSA CELL TUMOUR unil	1	0	0	0	1	0.2381	0.4878
LYMPHOMA LYMPHOBLASTIC TYP	1	0	0	0	0		
SEX CORD STROMAL TUMOR	1	2	2	2	0	0.9191	1.0000
Pancreas							
ADENOCARCINOMA	1	0	0	0	0		
ADENOMA ACINAR CELL	1	1	0	0	0	1.0000	1.0000
ADENOMA ISLET CELL	1	2	3	1	0	0.9551	1.0000
Adenoma/-carcinoma Islet Cell	1	2	3	1	0	0.9551	1.0000
ISLET CELL ADENOCARCINOMA	0	0	0	0	1	0.2577	0.5000
Parathyroids							
ADENOMA	0	0	1	0	0	0.7429	
Pituitary							
ADENOCARCINOMA PARS DISTALIS	1	5	2	0	1	0.9870	0.9899
ADENOMA PARS DISTALIS	25	21	21	23	18	0.6934	0.6448
Adenoma/-carcinoma Pars Dist.	26	26	23	23	19	0.9165	0.9124
Salivary glands							
ADENOCARCINOMA	0	1	0	0	0	1.0000	1.0000
Systemic							
Hemangioma	0	1	1	1	1	0.5601	0.7805
Hemangioma/-sarcoma	2	2	2	2	2	0.5553	0.7366
Hemangisarcoma	2	1	1	1	1	0.5601	0.7805
Thymus							
THYMOMA	4	2	1	0	1	0.7979	0.8902
THYMOMA malignant	0	0	1	0	0	0.7500	
Thyroids							
ADENOMA C CELL unilat	0	2	3	7	1	0.6529	0.8354
ADENOMA FOLLICUL CELL unil	0	2	1	0	1	0.7818	0.8752
C CELL CARCINOMA unilat	1	0	0	0	3	0.0182	0.1324
CARCINOMA FOLLICUL CELL uni	0	0	0	0	1	0.2381	0.4878
Tongue (incl base)							
SQUAMOUS CELL CARCINOMA	0	0	0	2	0	0.5507	

Table A.3.3. (cont.) Tumorgenicity in Female Rats

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Urinary bladder							
GRANULAR CELL TUMOUR	1	1	1	0	0	0.9398	1.0000
Uterus (incl cervix)							
ADENOCARCINOMA	2	2	4	3	2	0.6467	0.7064
ADENOMA (PAPILLARY)	0	2	0	1	0	0.9384	1.0000
Adenoma/Adenocarcinoma	2	4	4	4	2	0.8321	0.9044
CARCINOSARCOMA	0	1	0	0	0	1.0000	1.0000
ENDOMETRIAL STROMAL SARCOMA	0	0	0	1	0	0.4881	
GRANULAR CELL TUMOUR TYPE B	1	0	0	0	0		
HAEMANGIOSARCOMA	1	0	0	0	0		
POLYP GLANDULAR	1	2	1	0	2	0.5227	0.7064
POLYP ENDOMETRIAL STROMAL	5	10	8	4	5	0.9425	0.9064
Polyp Gland./Endo. Stromal	6	12	8	4	7	0.9144	0.8912
SCHWANNOMA MALIGNANT Type B	0	0	0	1	0	0.4286	

Table A.3.4. Tumorgenicity in Male Mice

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Adrenals							
ADENOMA SUBCAPS CELL unil	1	1	0	1	1	0.3457	0.7248
CORTICAL ADENOMA unilat	1	3	5	1	1	0.9258	0.9406
PHAEOCHROMOCYTOMA	0	1	1	0	0	0.9257	1.0000
Bone (os femoris with joi							
OSTEOSARCOMA GIANT CELL T	0	0	1	0	0	0.7294	
Brain (cerebrum)							
MALIGN SCHWANNOMA	1	0	0	0	0		
Caecum							
ADENOCARCINOMA	0	1	0	0	0	1.0000	1.0000
Coagulation gland seminal							
CYSTADENOMA	0	0	0	0	1	0.2588	0.4889
Duodenum							
ADENOCARCINOMA	1	0	0	0	0		
ADENOMA	0	0	0	1	0	0.6129	
Gall bladder							
ADENOMA	0	0	1	0	0	0.7294	
Haematopoietic system							
GRANULOCYTIC LEUKAEMIA	0	0	1	0	0	0.7294	
LYMPHOMA LYMPHOCYTIC TYPE	0	1	2	1	0	0.8647	1.0000
LYMPHOMA PLEOMORPHIC TYPE	3	2	4	1	1	0.8413	0.8691
Harderian glands							
ADENOMA PAPILLARY bilat	0	1	0	1	0	0.7101	1.0000
ADENOMA PAPILLARY unilat	1	1	0	1	2	0.1635	0.4605
ADENOMA unilat	0	3	1	2	0	0.9629	1.0000
Lesions (anal region)							
HAEMANGIOMA	0	0	0	0	1	0.1765	0.4615
Lesions (head)							
MALIGN SCHWANNOMA	1	0	0	0	0		

Table A.3.4. (cont.) Tumorgenicity in Male Mice

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctrl
Liver							
HAEMANGIOMA	1	1	0	0	0	1.0000	1.0000
HAEMANGIOSARCOMA	1	1	1	1	0	0.8222	1.0000
HEPATOCELLULAR ADENOMA	3	5	2	3	0	0.9862	1.0000
HEPATOCELLULAR CARCINOMA	6	7	3	4	2	0.9141	0.9787
Hepat. Adenoma/-carcinoma	9	12	5	7	2	0.9913	0.9969
MESOTHELIOMA	0	1	0	0	0	1.0000	1.0000
Lungs with bronchi							
ADENOMA BRONCHIOLO ALVEOL	0	2	4	1	4	0.2818	0.4679
Adenoma/-carcinoma Bronchio.	6	4	7	1	7	0.2068	0.2238
CARCINOMA BRONCHIOLO ALV	6	2	3	0	3	0.3049	0.4679
Lymph node (mesenteric)							
HAEMANGIOMA	1	0	0	0	0		
Mononuclear phagocytis ti							
HISTIOCYTIC SARCOMA	1	0	0	1	0	0.5000	
Nasal cavity with nasopha							
ODONTOMA	0	0	0	1	0	0.4588	
Pancreas							
ADENOMA ISLET CELL	1	0	0	0	2	0.0749	0.2561
Pituitary							
ADENOCARCINOMA PARS DISTALS	0	0	1	0	0	0.7478	
ADENOMA PARS DISTALIS	1	0	1	0	2	0.1131	0.2442
Adenoma/-carcinoma Pars Dist.	1	0	2	0	2	0.1959	0.2442
Spleen							
HAEMANGIOSARCOMA	1	0	0	1	0	0.4690	
Stomach (2 sections)							
ADENOCARCINOMA	0	1	0	0	0	1.0000	1.0000
OSTEOSARCOMA	0	1	0	0	0	1.0000	1.0000
Systemic							
Hemangioma	2	1	0	0	1	0.3262	0.7308
Hemangioma/-sarcoma	4	2	1	2	1	0.5759	0.8624
Hemangisarcoma	2	1	1	2	0	0.7671	1.0000
Testicle							
ADENOMA LEYDIG CELL unilat	0	1	1	0	1	0.5176	0.7160
CARCINOMA RETE TESTIS	0	0	1	0	0	0.7294	
HAEMANGIOMA unilat	0	1	0	0	0	1.0000	1.0000
Thymus							
THYMOMA	0	0	3	2	0	0.7754	
Thyroids							
ADENOMA FOLLICUL CELL unil	1	1	0	0	0	1.0000	1.0000
Urinary bladder							
HAEMANGIOMA CAVERNOUS	0	0	0	1	0	0.5946	
Zymbal glands							
KERATOACANTHOMA	0	0	0	1	0	0.5789	
MENINGIOMA	0	1	0	0	0	1.0000	1.0000
MYXOMA	1	0	0	0	0		

Table A.3.5. Tumorgenicity in Female Mice

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctr1
Adrenals							
ADENOMA SUBCAPS CELL unil	0	0	0	0	1	0.2549	0.5778
PHAEOCHROMOCYTOMA	0	0	1	0	0	0.8137	
Brain (cerebrum)							
CHOROID PLEXUS CARCINOMA	0	0	0	1	0	0.4118	
Haematopoietic system							
GRANULOCYTIC LEUKAEMIA	0	1	0	0	2	0.1544	0.5458
LYMPHOMA LYMPHOBLASTIC TYPE	0	0	0	1	0	0.5000	
LYMPHOMA LYMPHOCYTIC TYPE	1	2	1	0	3	0.1517	0.4677
LYMPHOMA PLEOMORPHIC TYPE	12	7	6	6	7	0.4456	0.5748
Harderian glands							
ADENOCARCINOMA unilat	0	0	0	1	1	0.1644	0.4783
ADENOMA PAPILLARY unilat	1	1	0	0	2	0.1590	0.6184
Kidneys							
MALIG FIBR HISTIOC (MFH)	0	1	0	0	0	1.0000	1.0000
Lesions (abdominal cavity							
HAEMANGIOMA	0	1	0	0	0	1.0000	1.0000
Lesions (head)							
ADENOCARCINOMA HARDER	0	0	0	0	1	0.2408	0.4842
Lesions (hind leg)							
ADENOCARCINOMA mamma	0	0	0	1	0	0.4826	
MALIG FIBR HISTIOC (MFH)	0	0	0	0	1	0.2500	0.5385
OSTEOSARCOMA	1	0	0	0	0		
Lesions (shoulder)							
ADENOCARCINOMA mamma	0	0	0	1	0	0.4823	
Liver							
CHOLANGIOCARCINOMA	0	1	0	0	0	1.0000	1.0000
HAEMANGIOSARCOMA	0	0	1	1	0	0.6350	
HEPATOCELLULAR CARCINOMA	0	0	1	1	1	0.2608	0.4348
Hepat. Adenoma/-carcinoma	0	0	1	1	1	0.2608	0.4348
Lungs with bronchi							
ADENOMA BRONCHIOLO ALVEOL	1	3	2	0	2	0.6215	0.8373
Adenoma/-carcinoma Bronchio.	2	5	3	3	2	0.8559	0.9642
CARCINOMA BRONCHIOLO ALV	1	2	1	3	0	0.8804	1.0000
Mammary gland							
ADENOCARCINOMA	0	0	1	0	0	0.7797	
RHABDOMYOSARCOMA	0	0	1	0	0	0.7838	
Mononuclear phagocytis ti							
HISTIOCYTIC SARCOMA	4	4	4	6	2	0.7810	0.8423
Ovaries							
CYSTIC PAPILLARY ADENOMA	2	1	0	1	0	0.6844	1.0000
GRANULOSA CELL TUMOR bilat	0	0	0	0	1	0.1250	0.2857
GRANULOSA CELL TUMOR unilat	1	0	0	0	0		
HAEMANGIOMA unilat	0	0	1	0	0	0.6875	
SEX CORD STROMAL TUMOR unil	0	0	0	0	1	0.2475	0.5682
TUBULOSTROMAL ADENOMA	0	0	0	0	1	0.2632	0.4348
Pancreas							
ADENOMA ACINAR CELL	0	1	0	0	0	1.0000	1.0000
Parathyroids							
ADENOMA	0	0	0	0	1	0.2131	0.5200

Table A.3.5. (cont.) Tumorgenicity in Female Mice

	Incidence:					p-values:	
	Ctr0	Ctr1	Low	Med	High	Trend	Hi vs Ctrl
Pituitary							
ADENOMA PARS DISTALIS	1	1	2	0	1	0.6617	0.8273
Adenoma/-carcinoma Pars Dist.	1	1	2	0	1	0.6617	0.8273
Spleen							
HAEMANGIOSARCOMA	0	1	0	0	0	1.0000	1.0000
Stomach (2 sections)							
SQUAMOUS CELL CARCINOMA	1	0	0	0	0		
Systemic							
Hemangioma	0	2	0	0	0	1.0000	1.0000
Hemangioma/-sarcoma	0	3	1	1	0	0.9577	1.0000
Hemangisarcoma	0	1	1	1	0	0.8299	1.0000
Thymus							
THYMOMA	0	3	1	0	1	0.7835	0.9492
Uterus (incl cervix)							
HAEMANGIOMA	0	1	0	0	0	1.0000	1.0000
LEIOMYOSARCOMA	0	1	0	0	1	0.4302	0.7467
MALIG FIBR HISTIOC (MFH)	1	0	0	0	0		
POLYP GLANDULAR	4	1	1	1	2	0.2545	0.3834
POLYP ENDOMETRIAL STROMAL	0	1	2	2	1	0.5787	0.6526
Polyp Gland./Endo. Stromal	4	2	3	3	3	0.3860	0.3354
Vagina							
LEIOMYOMA	0	0	0	1	0	0.5000	

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Appendix 4. References

Bailer, A. and Portier, C. (1988), "Effects of Treatment-Induced Mortality on Tests for Carcinogenicity in Small Samples", *Biometrics*, **44**, 4, 417-431.

Bieler, G.S., and Williams, R.L. (1993), "Ratio Estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity", *Biometrics*, **49**, 4, 793-801.

Chu, K.C., Ceuto, C., and Ward, J.M. (1981), Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, *Journal of Toxicology and Environmental Health*, 8, 251-280.

Haseman, J. K. (1983), A Reexamination of False-positive Rates for Carcinogenicity Studies, *Fundamental and Applied Toxicology*, 3, 334-339.

Ibrahim, J.G., Chen, M.-H., and Sinha, D. (2001), *Bayesian Survival Analysis*, Springer Verlag, New York.

Lin, K. K. and Ali, M.W. (2006), Statistical Review and Evaluation of Animal Tumorigenicity Studies, *Statistics in the Pharmaceutical Industry,Third Edition*, edited by C.R. Buncher and J.Y. Tsay, Marcel Dekker, Inc. New York.

Lin, K. K. and Rahman, M.A. (1998), Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs, *Journal of Biopharmaceutical Statistics*. 8(1), 1-15.

McConnell, E.E., Solleveld, H.A., Swnberg, J.A., and Boorman, G.A. (1986), Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies, *Journal of the National Cancer Institute*. 76, 283-289.

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parrish, S., Peto, J., Richards, S., and Wahrendorf, J. (1980). Guidelines for sample sensitive significance tests for carcinogenic effects in long-term animal experiments, *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, supplement 2: Long term and Short term Screening Assays for Carcinogens: A Critical Appraisal*, International Agency for Research Against Cancer, 311-426.

STP Peto Working Group (2002), Statistical Methods for Carcinogenicity Studies, *Toxicologic Pathology*. 30 (3), 403-414.

U.S. Department of Health and Human Services (2001), *Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (DRAFT GUIDANCE)*, Center for Drug Evaluation and Research, Food and Drug Administration.

/s/

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3/10/2008 09:24:17 AM
BIOMETRICS

Karl Lin
3/10/2008 09:34:03 AM
BIOMETRICS
Concur with review