Table 3: Patient Disposition

Parameter	Placebo	LCM 400mg/day	LCM 800mg/day	Moxi	Total
	n (%)				
Randomized	62	60	71	54	247
Randomized and treated	62 (100)	60 (100)	71 (100)	54 (100)	247 (100)
Completed trial	55 (88.7)	57 (95.0)	54 (76.1)	54 (100)	220 (89.1)
Prematurely discontinued	7 (11.3)	3 (5.0)	17 (23.9)	0	27 (10.9)
Reason for discontinuation					
Adverse event	0	0	2 (2.8)	0	2 (0.8)
Subject withdrew consent	4 (6.5)	1 (1.7)	11 (15.5)	0	16 (6.5)
Other	3 (4.8)	2 (3.3)	4 (5.6)	0	9 (3.6)

LCM = lacosamide; Moxi = moxifloxacin
Reproduced from page 64 of sponsor's study report

Randomized Set (RS): All randomized subjects were included in the RS.

Safety Set (SS) All randomized subjects who received at least 1 dose of trial medication were included in the SS.

Pharmacodynamic Set (PDS): All SS subjects who completed through Day 3 in the moxifloxacin group and through Day 6 in the lacosamide and placebo groups and had a sufficient H-12 data to calculate reliable estimates for the pharmacodynamic parameters were included in the PDS. Any subject with a major protocol deviation that would render the ECG data unreliable or render the data incomparable among subject groups was excluded from the PDS. The set of subjects that comprised the PDS was defined prior to unblinding. Subjects were replaced if they did not complete through Day 3 for subjects assigned to moxifloxacin or through Day 6 for subjects assigned to either placebo or lacosamide, including completion of the H-12 assessment on Day 3/6. Subjects who were replaced were excluded from the PDS and, therefore, were excluded from the primary analysis.

All randomized subjects received at least 1 dose of trial medication and therefore were included in the SS. Twenty-seven subjects discontinued from the trial prior to completing the dosing regimen and thus were not included in the PDS. An additional 6 subjects were missing H-12 ECG data at greater than 3 time points on primary ECG recording days; these subjects were classified as major protocol deviators and were excluded from the PDS.

Table 4 provides a summary of baseline demographics for the study patients by randomized group.

Table 4: Baseline Demographics

Parameter	Placebo N=62	LCM 400mg/day N=60	LCM 800mg/day N=71	Moxi N=54	All subjects N=247
Age (years)					
Mean (SD)	24.1 (6.1)	24.7 (6.4)	24.9 (6.7)	25.1 (7.3)	24.7 (6.6)
Min, Max	18-45	18-44	18-43	18-44	18-45
Sex					
Male (n[%])	30 (48.4)	27 (45.0)	28 (39.4)	27 (50.0)	112 (45.3)
Female (n[%])	32 (51.6)	33 (55.0)	43 (60.6)	27 (50.0)	135 (54.7)
Race					
White (n[%])	51 (82.3)	54 (90.0)	65 (91.5)	48 (88.9)	218 (88.3)
Black (n[%])	2 (3.2)	1 (1.7)	3 (4.2)	3 (5.6)	9 (3.6)
Asian (n[%])	2 (3.2)	3 (5.0)	1 (1.4)	2 (3.7)	8 (3.2)
Other (n[%])	7 (11.3)	2 (3.3)	2 (2.8)	1 (1.9)	12 (4.9)
Height (cm)					
Mean (SD)	171.6 (9.0)	170.3 (8.6)	170.0 (8.5)	172.0 (9.1)	170.9 (8.8)
Min, Max	150-191	150-191	152-188	152-193	150-193
Weight (kg)					
Mean (SD)	72.94 (11.89)	72.90 (12.09)	69.36 (11.85)	75.81 (13.04)	72.53 (12.33)
Min, Max	50.4-109.4	47.7-104.4	47.2-96.2	53.6-109.4	47.2-109.4
BMI (kg/m^2)					
Mean (SD)	24.70 (3.04)	25.05 (3.13)	23.91 (3.05)	25.52 (3.22)	24.74 (3.15)
Min, Max	19.0-32.0	19.7-31.4	18.9-31.0	19.0-32.0	18.9-32.0

BMI = body mass index; LCM = lacosamide; Max = maximum; Min = minimum; Moxi = moxifloxacin; SD = standard deviation; SS = Safety Set

Reproduced from p 67 out of 8001 of sponsor's study report

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary analysis was based on a non-inferiority comparison of each LACOSAMIDE group with placebo using 1-sided 95% confidence intervals (or, equivalently, the upper limits of 2-sided 90% confidence intervals) for maximum time-matched change from Baseline in QTcI (calculated by taking the maximum of all time-matched changes for each subject for each day).

Confidence intervals were produced using an analysis of covariance (ANCOVA) model with effects for treatment and gender, and time-matched baseline QTcI as a covariate. Additionally, 2-sided confidence intervals for maximum time-matched change from baseline in QTcI were presented within each treatment group.

For ECG parameters, the baseline values were obtained from the H-12 assessment on Day -1. For time-matched changes, the baseline at each time point was the median of the 3 values obtained at each time point. The primary variable for this trial was the maximum time-matched change in QTcI from Baseline to Day 3 for the moxifloxacin group and Day 6 for the placebo and lacosamide groups. All analyses of the primary variable were based on data from the H-12 recorder. The primary analysis was based on a non-inferiority comparison of each lacosamide group with placebo using 1-sided 95% confidence intervals (or, equivalently, the upper limits of 2-sided 90% confidence intervals). Confidence intervals were produced using an ANCOVA model with effects for treatment and gender, and time-matched baseline QTcI as a covariate. The statistical model was fit with all 4 treatment groups; therefore, the estimate of the variance was a pooled estimate obtained from all 4 treatment groups. Time-matched baseline QTcI was the Baseline value from the time point on Day -1, which corresponds to the time point on Day 6 or Day 3 at which the maximum change occurs.

The sponsor also did a time averaged analysis. For time-averaged changes, the baseline value was obtained as follows: 1) the median of the 3 values at each time point on Day -1 was obtained, and 2) these 12 values were averaged to obtain the time-averaged baseline value.

The difference in the maximum time-matched change from Baseline in QTcI between the 400 mg/day lacosamide group and placebo was -4.3 and between the 800 mg/day lacosamide group and placebo was -6.3. In both cases, the upper limit of the 2-sided 90% CI (-0.5 and -2.5 for 400 mg/day lacosamide and 800 mg/day lacosamide, respectively) was below the 10 ms non-inferiority margin, thereby demonstrating that there is no relevant increase of QTcI caused by lacosamide. The sponsor claimed that assay sensitivity was demonstrated since the mean difference between moxifloxacin and placebo was 10.4 ms and the lower 95% confidence bound was >0, thereby showing a statistically significant effect over placebo. Results were similar for the SS and for males and females.

The statistical analysis of the maximum time-matched change on Day 6 (Day 3 for moxifloxacin) in QTcI is presented in the following table. The sponsor reported the 2-sided 90% confidence interval, as well as the 95% interval.

Table 5: Maximum* time-matched change on Day 6 (Day 3 for moxifloxacin) (PDS)

Treatment	n	Endpoint LSMean	Comparison	Treatment Difference (SE)	90% CI[a]	95% CI[a]
Placebo	54	20.9				
LCM 400mg/day	56	16.6	B – A	-4.3 (2.2)	-8.0, -0.5	-8.7, 0.2
LCM 800mg/day	52	14.6	C – A	-6.3 (2.3)	-10.0, -2.5	-10.8, -1.7
Moxi	52	31.3	D – A	10.4 (2.3)	6.6, 14.2	5.9, 14.9

Note: A = placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = moxifloxacin
Note: p-values and confidence intervals are based on an ANCOVA model with effects for treatment and gender and time-matched Baseline QTcI as a covariate.
Note: Maximum time-matched change from Baseline to Day 3 for moxifloxacin group.
ANCOVA = analysis of covariance; CI = confidence interval of mean; LSMeans = least squares mean; LCM = lacosamide; Moxi = moxifloxacin; PDS = pharmacodynamic set; SE = standard error
a. Confidence intervals are for the treatment differences

*Mean of maximum over time within each individual subject

Table 6 and Table 7 give the results by hour on day 3 and day 6, respectively.

Table 6: Non-Inferiority Analysis of Time-Matched Change in QTcI (ms) by Day and Time - ANCOVA Model- Pharmacodynamic Set

Time Point	LS Means				Treatment Difference			90% Confidence Intervals		
	A	B	C	D	B - A	C - A	D - A	B - A	C - A	D - A
Day 3										
1h	-5.7	-10.0	-10.5	5.7	-4.2	-4.8	11.5	(-8.4, -0.1)	(-9.0, -0.5)	(7.3, 15.7)
2h	-9.5	-10.4	-11.2	3.2	-0.9	-1.7	12.6	(-5.9, 4.1)	(-6.8, 3.3)	(7.6, 17.7)
3h	-1.2	-5.8	-5.8	11.1	-4.3	-4.4	12.2	(-8.9, 0.3)	(-9.0, 0.3)	(7.6, 16.9)
4h	2.8	-0.0	-3.7	16.2	-2.9	-6.7	14.2	(-6.7, 2.7)	(-10.5, -3.0)	(9.4, 19.1)
5h	-7.6	-10.3	-8.8	5.4	-2.6	-1.2	13.0	(-7.2, 1.9)	(-5.9, 3.5)	(8.3, 17.7)
6h	-5.1	-9.1	-15.1	1.8	-4.0	-10.0	6.9	(-9.1, 1.0)	(-15.2, -4.8)	(1.7, 12.0)
10h	-4.6	-8.8	-7.9	8.5	-0.8	-2.8	12.1	(-6.6, 5.3)	(-7.8, 1.3)	(6.6, 17.7)
12h	-10.2	-11.7	-12.4	-3.4	-1.5	-2.2	6.8	(-6.3, 3.2)	(-7.1, 2.7)	(1.9, 11.6)
14h	-5.4	-8.2	-9.8	1.2	-2.7	-4.3	6.6	(-7.2, 1.7)	(-8.9, 0.3)	(2.0, 11.2)
16h	-2.6	-7.2	-11.0	2.1	-4.6	-8.5	4.7	(-9.0, -0.2)	(-13.0, -4.0)	(0.2, 9.2)
18h	-1.6	-4.8	-10.1	7.8	-3.3	-8.6	9.4	(-6.9, 0.4)	(-12.2, -4.9)	(5.6, 13.0)
24h	3.2	-4.2	-2.3	8.9	-7.5	-5.5	0.7	(-12.1, -2.8)	(-10.2, -0.7)	(-4.1, 5.5)

Note: A = Placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = Moxifloxacin
Note: Non-inferiority comparisons are based on the upper limits of 90% CIs for the difference between LCM groups and placebo using a non-inferiority bound of 10ms.
Note: Least squares means and confidence intervals are based on ANCOVA with effects for treatment, gender and time-matched Baseline value as a continuous covariate.
The ANCOVA model was fit separately at each time point.
Note: Only Day 3 and Day 6 are analyzed. Analysis for Day 6 is based on data from Day 3 for Moxifloxacin.

Table 7: Non-Inferiority Analysis of Time-Matched Change in QTcI (ms) by Day and Time - ANCOVA Model - Pharmacodynamic Set

Time Point	LS Means				Treatment Difference			90% Confidence Intervals		
	A	B	C	D	B - A	C - A	D - A	B - A	C - A	D - A
Day 6										
1h	-2.8	-9.6	-10.8	5.8	-6.8	-8.0	8.6	(-11.6, -2.0)	(-12.8, -3.7)	(4.8, 12.9)
2h	3.0	-6.2	-4.9	3.1	-9.1	-7.9	0.1	(-13.6, -4.7)	(-12.4, -3.3)	(-4.4, 4.7)
3h	-2.8	-2.8	-8.0	11.0	0.2	-5.2	13.8	(-4.5, 5.0)	(-10.0, -0.4)	(9.0, 18.6)
4h	-8.7	-2.1	-6.1	16.2	1.6	-2.4	19.8	(-2.6, 5.8)	(-6.7, 1.9)	(15.5, 24.1)
6h	-9.8	-11.9	-11.9	5.4	-2.6	-2.6	14.7	(-7.5, 2.4)	(-7.6, 2.4)	(9.7, 19.7)
8h	-9.4	-10.3	-11.6	1.8	-0.9	-2.2	11.2	(-5.6, 3.8)	(-7.0, 2.6)	(6.4, 16.0)
10h	-0.8	-4.8	-8.4	8.6	-3.9	-7.5	9.4	(-8.8, 0.9)	(-12.5, -2.6)	(4.5, 14.4)
12h	-8.1	-9.2	-11.5	-2.4	-0.2	-2.5	5.7	(-4.9, 4.6)	(-7.3, 2.3)	(0.8, 10.5)
14h	-1.3	-3.6	-5.0	1.2	-2.4	-3.7	2.5	(-7.0, 2.2)	(-8.4, 1.0)	(-2.3, 7.2)
16h	-14.1	-17.2	-15.1	2.2	-3.2	-1.0	16.3	(-7.8, 1.4)	(-8.7, 0.7)	(11.6, 21.0)
18h	-2.2	-3.7	-9.8	7.8	-0.6	-6.7	11.0	(-4.8, 3.7)	(-11.0, -2.3)	(6.7, 15.3)
24h	1.9	-2.8	-4.8	8.9	-4.7	-6.7	2.0	(-10.1, 0.7)	(-12.1, -1.3)	(-3.5, 7.5)

Note: A = Placebo, B = LCM 400mg/day, C = LCM 800mg/day, D = Moxifloxacin
Note: Non-inferiority comparisons are based on the upper limits of 90% CIs for the difference between LCM groups and placebo using a non-inferiority bound of 10ms.
Note: Least squares means and confidence intervals are based on ANCOVA with effects for treatment, gender and time-matched Baseline value as a continuous covariate.
The ANCOVA model was fit separately at each time point.
Note: Only Day 3 and Day 6 are analyzed. Analysis for Day 6 is based on data from Day 3 for Moxifloxacin.

4.2.7.2.2 Categorical Analysis

A summary of the number of absolute and change from Baseline outliers in QTcI by day and time is presented in the following table.

Table 8: Summary of subjects with a new onset QTcI outlier value during the Treatment Phase (Pharmacodynamic Set)

Parameter	Placebo N=54	LCM 400mg/day N=56	LCM 800mg/day N=52	Moxi N=52
	n (%)			
QTcI				
450ms to <480ms	4 (7.4)	3 (5.4)	1 (1.9)	8 (15.4)
480ms to <500ms	0	0	0	0
≥500ms	0	0	0	0
QTcI				
Increase of 30 to <60ms	20 (37.0)	15 (26.8)	10 (19.2)	28 (53.8)
Increase of ≥60ms	1 (1.9)	0	0	4 (7.7)

LCM = lacosamide; Moxi = moxifloxacin; PDS = pharmacodynamic set

Reproduced from page 78 of sponsor's study report

There were no ECGs with a QTcI of 480 ms or greater at any post-Baseline time point that were not present at Baseline. The percentage of subjects with new onset values for QTcI of ≥ 450ms was 7, 5, 2, and 15 in the placebo, 400 mg/day lacosamide, 800 mg/day lacosamide, and moxifloxacin groups, respectively. One subject in the placebo group and 4 subjects in the moxifloxacin group had changes from baseline of ≥ 60ms in QTcI. No subject in either lacosamide group had a change from baseline in QTcI that was 60 ms or greater at any time point during the trial. The percentage of subjects with increases in QTcI that were 30 to 60 ms was higher in the moxifloxacin group and placebo groups, 54% and 37%, respectively, compared with 27% and 19% in the 400 mg/day and 800 mg/day lacosamide groups, respectively. The corresponding percentages with QTcI increases between 30 and 60 ms in the all randomized set were 56, 32, 25, 19, for Moxifloxacin, placebo, 400 mg/day lacosamide and 800 mg/day lacosamide, respectively.

4.2.7.3 Safety Analysis

No subject died. 1 subject had an SAE, a spontaneous abortion 9 days following her last dose of 800 mg of lacosamide. 1 subject had a 2 minute episode of syncope about 12 hours after being administered 800 mg of lacosamide on day 4; the sponsor reports no ECG being available at the time of occurrence.

27 subjects failed to complete the study (see Table 3); 15 of these were in the lacosamide 800 mg treatment group, 3 in the lacosamide 400 mg treatment group, 7 in the placebo group, and none in the moxifloxacin group. The reasons are as follows:

- 2 subjects (both in the 800 mg lacosamide treatment group and both female) were withdrawn due to AEs; 1 for neck pain and the other for hematemesis due to Mallory-Weiss tear.
- 8 additional female subjects in the 800 mg qd lacosamide treatment group and 1 female in the 400 mg qd group withdrew consent while experiencing AEs. All of these were related to some combination of dizziness, nausea and vomiting. The sponsor does not report any abnormalities or ECG for any of these subjects.
- 3 subjects in the 800 mg qd lacosamide treatment group and 4 subjects in the placebo group withdrew consent without ongoing AEs

- 4 subjects in the 800 mg qd lacosamide treatment group, 1 in the 400 mg qd group, and 3 subjects in the placebo group withdrew for "other"

AEs were experienced more frequently by subjects in the 800 mg/day lacosamide treatment group and consisted primarily of events in the nervous system. 274 of the 312 AEs were assessed by the investigator as mild and the rest as moderate. The most common events in the 800mg/day lacosamide group were dizziness (54.9% of subjects), nausea (26.8%), headache (22.5%), hypoesthesia oral (21. %), and feeling drunk (15.5%).

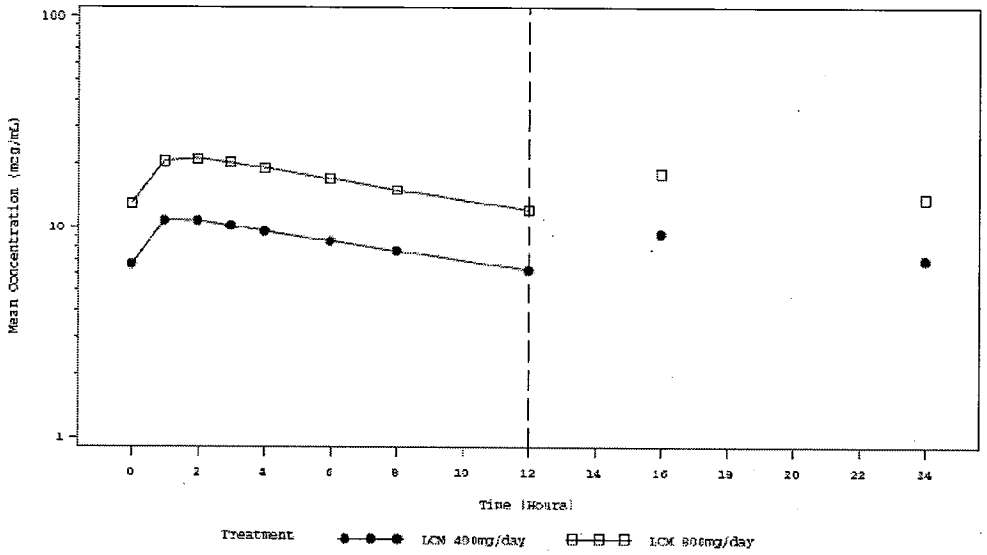
Reviewer's comment: Many of the subject withdrawals appear to be due to poor tolerability of the 800 mg dose of lacosamide. However, 15 subjects (~7% of the total) withdrew for unclear reason. For a pharmacokinetic study of healthy subjects, this number is quite high and may affect the reliability of the data.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The mean lacosamide plasma concentration-time profiles after multiple oral administrations of 400 mg/day and 800 mg/day over 6 days are shown in Figure 1.

Figure 1: Mean Plasma Concentration-Time Profiles of Lacosamide by Treatment on day 6



Reproduced from sponsor's Figure 4.3 on page 890 in study report SP640

The main metabolite for lacosamide is SPM12809. The mean SPM12809 plasma concentration-time profiles after multiple oral administrations of 200 mg bid and 400 mg bid over 6 days are shown in Figure 2

Figure 2: Mean Plasma Concentration-Time Profiles of the Main Metabolite for Lacosamide (SPM12809) by Treatment on day 6

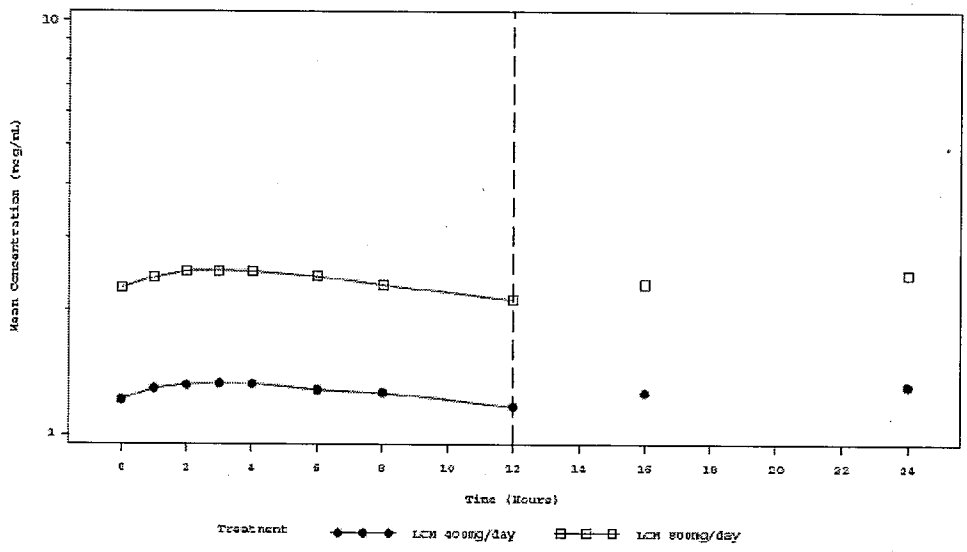
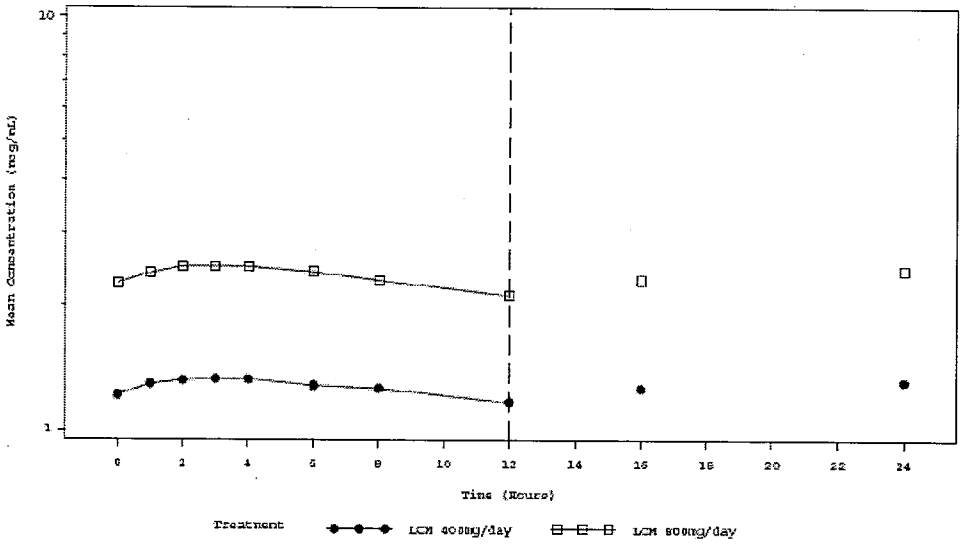


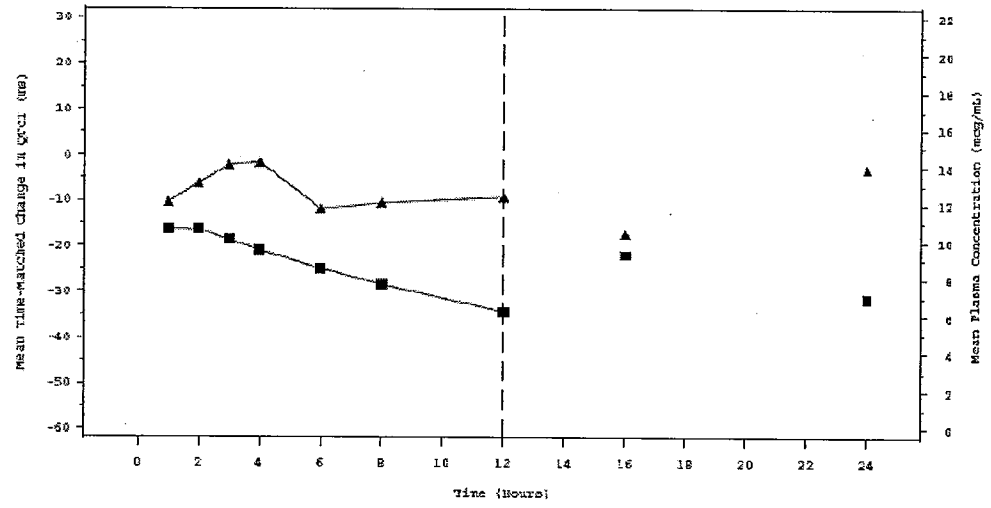
Figure 2: Mean Plasma Concentration-Time Profiles of the Main Metabolite for Lacosamide (SPM12809) by Treatment on day 6



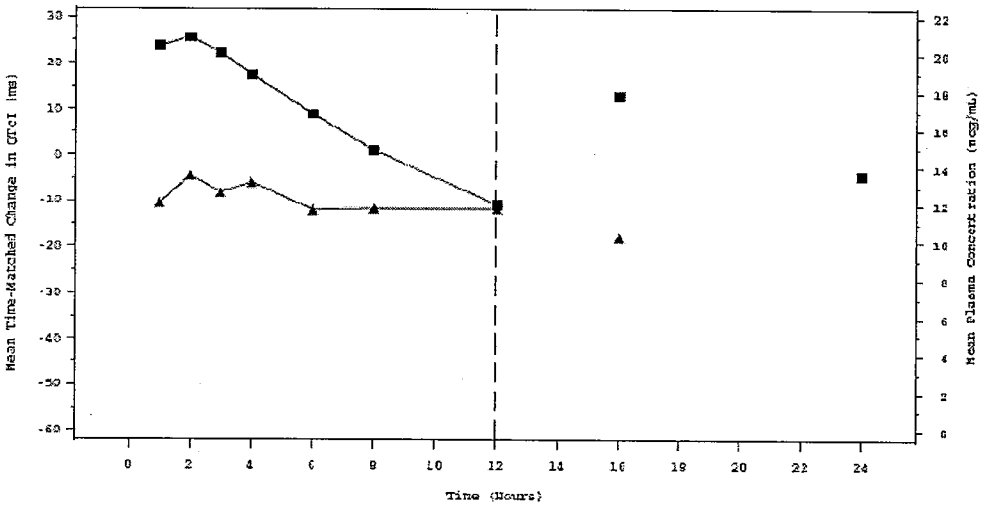
Reproduced from sponsor's Figure 4.4 on page 891 in study report SP640

The mean time-matched change from baseline in QTcI and mean plasma concentration of lacosamide after multiple oral dosing of 400 mg/day (top) and 800 mg/day (bottom) are shown in Figure 3.

Figure 3: Mean Time-Matched Change from Baseline in QTcI and Mean Plasma Concentration-Time Profiles for Lacosamide by Treatment on day 6



Note: Subject was dosed at 0h and 12h time points.
▲▲▲Mean Time-Matched Change in QTcI (ms) ■■■Mean Plasma Concentration (mcg/mL)



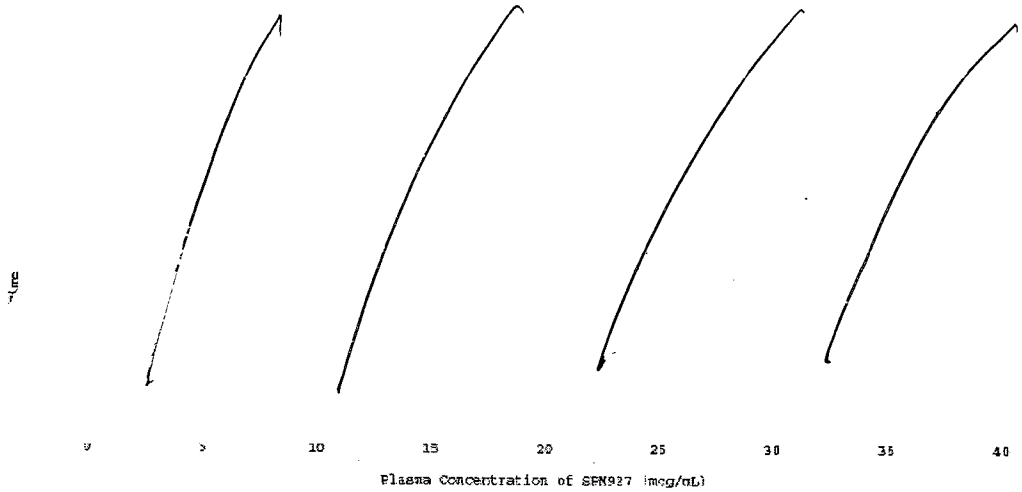
Note: Subject was dosed at 0h and 12h time points.
▲▲▲Mean Time-Matched Change in QTcI (ms) ■■■Mean Plasma Concentration (mcg/mL)

Reproduced from Sponsor's Figure 5.1 on page 892 and 893 in study report SP640

4.2.7.4.2 Exposure-Response Analysis

A simple linear model was developed to evaluate the relationship between time-matched change from baseline QTcI and plasma concentration of lacosamide. The results are illustrated in Figure 4. The linear correlation between time-matched change from baseline QTcI was very weak.

Figure 4: Time-Matched Change from Baseline in QTcI vs. Plasma Concentration of Lacosamide



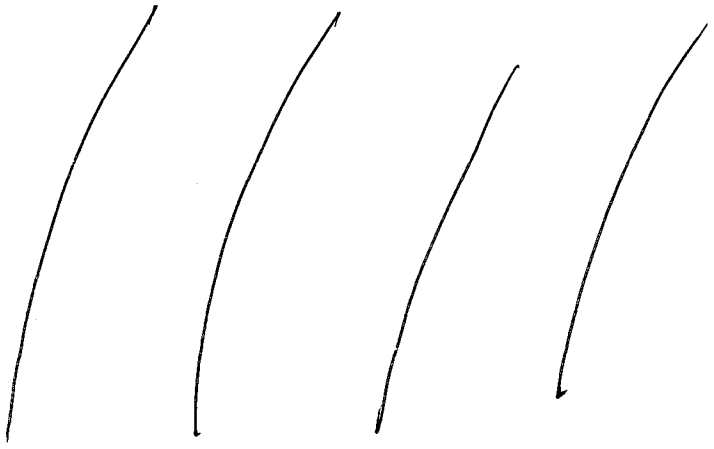
b(4)

Reproduced from Sponsor's Figure 6.1 on page 906 in study report SP640

APPEARS THIS WAY
ON ORIGINAL

According to the sponsor, there appeared to be a small increase in the PR interval with increasing concentration of lacosamide (see Figure 5)

Figure 5: Time-Matched Change from Baseline in PR vs. Plasma Concentration of Lacosamide



b(4)

Reproduced from Sponsor's Figure 6.5 on page 910 in study report SP640

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The sponsor designated the QTcI as the primary QT assessment. $QTcI = QT/(RR)^{\beta}$ where the coefficient β was derived, separately for each subject, by regression of log QT on log RR using only the baseline ECG data.

There were no time points at which the 1-sided 95% upper bound for the difference between either of the lacosamide treatment groups and the placebo group exceeded 10 ms in terms of the change in QTcI. The same results were also confirmed using QTcB, and QTcF. Assay sensitivity was demonstrated with Moxifloxacin since at multiple time points, the lower bound of 90% CI is above 5 ms; however, no multiple endpoints were adjusted though for the assay sensitivity analysis.

Figure 6 shows the baseline corrected difference in changes in QTcI between moxifloxacin and placebo over time on day 3 as estimated by the ANCOVA model at each timepoint.

APPEARS THIS WAY
ON ORIGINAL

Figure 6: LS Means and 2-sided 90% Bounds for Moxifloxacin ΔΔQTcIs on Day 3 (All Randomized Set)

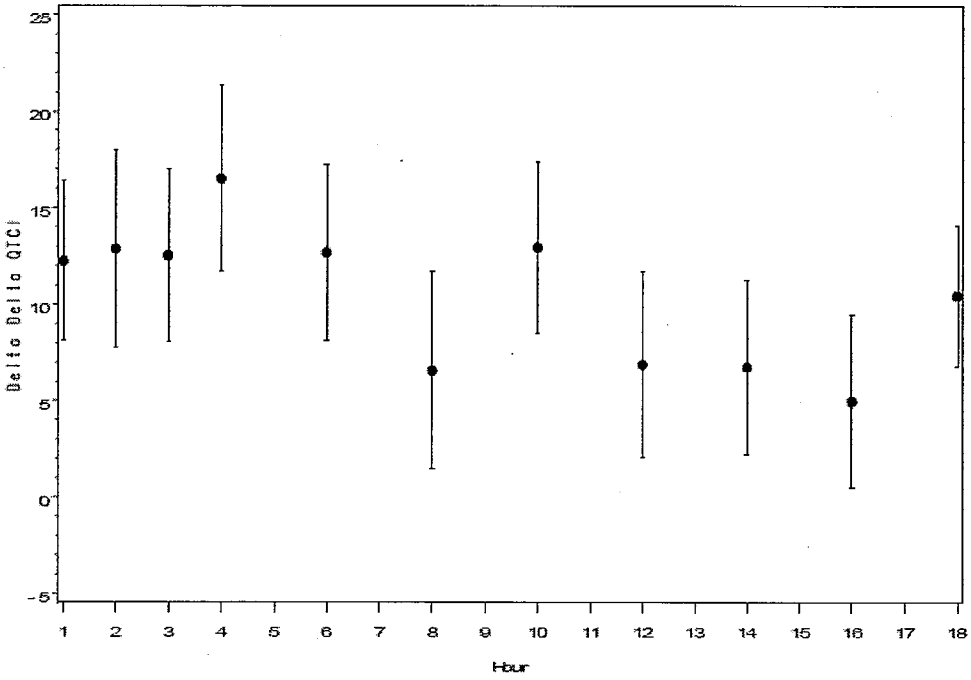


Table 9 provides the LS mean changes in QTcI for each day and each timepoint based on the ANCOVA model in the all randomized data set.

Table 9: Changes from baseline in QTcI in the All Randomized Set (FDA)

		Placebo		Lacosamide 400 mg				Lacosamide 800 mg				Moxifloxacin			
Day	Hour	N	LSMEAN (SE)	N	LSMEAN (SE)	Δ from Placebo	90% UB	N	LSMEAN (SE)	Δ from Placebo	90% UB	N	LSMEAN (SE)	Δ from Placebo	90% LB
1	1	61	-6.4 (2.1)	60	-8.9 (2.1)	-2.5	1.6	70	-9.3 (2)	-2.9	1.1	52	-4.2 (2.3)	2.1	-2.2
1	2	60	-4.9 (2.2)	59	-8.5 (2.2)	-3.6	0.8	70	-9.9 (2.1)	-5	-0.8	54	-0.2 (2.3)	4.7	0.3
1	3	61	-0.7 (1.9)	59	-5.6 (2)	-4.9	-1.1	70	-2.7 (1.8)	-2	1.6	54	10.9 (2)	11.6	7.7
1	4	60	0.3 (2.2)	54	-5 (2.3)	-5.3	-0.8	68	-3.8 (2.1)	-4	0.2	53	11.2 (2.4)	11	6.5
1	6	62	-5.9 (2.2)	57	-7.4 (2.3)	-1.6	2.9	70	-5.2 (2.1)	0.7	4.9	54	-3.3 (2.4)	2.5	-2
1	8	62	-6.1 (2.6)	57	-7.4 (2.7)	-1.4	3.7	70	-6.9 (2.4)	-0.8	4.1	53	-0.9 (2.8)	5.1	-0.1
1	10	62	-8.5 (1.9)	58	-8.9 (2)	-0.4	3.4	70	-9.4 (1.8)	-1	2.7	54	-2.3 (2.1)	6.2	2.3
1	12	61	-8 (2)	57	-11.6 (2.1)	-3.5	0.4	70	-7.5 (1.9)	0.5	4.3	53	-3.7 (2.1)	4.3	0.3

		Placebo		Lacosamide 400 mg				Lacosamide 800 mg				Moxifloxacin			
Day	Hour	N	LSMEAN (SE)	N	LSMEAN (SE)	Δ from Placebo	90% UB	N	LSMEAN (SE)	Δ from Placebo	90% UB	N	LSMEAN (SE)	Δ from Placebo	90% LB
1	14	61	-0.7 (2)	57	-6.9 (2.1)	-6.2	-2.3	70	-6.3 (1.9)	-5.5	-1.8	53	6.5 (2.1)	7.2	3.2
1	16	61	-2.1 (2.1)	57	-7.1 (2.1)	-5	-0.9	69	-8.2 (1.9)	-6.1	-2.3	53	2.9 (2.2)	5	0.8
1	18	59	-5.2 (1.9)	56	-6.8 (2)	-1.5	2.3	68	-5.7 (1.8)	-0.5	3.2	53	4.6 (2)	9.9	6
3	1	57	-6.5 (2.1)	57	-10 (2.1)	-3.5	0.5	65	-10.1 (1.9)	-3.6	0.3	52	5.8 (2.2)	12.3	8.1
3	2	56	-10 (2.6)	57	-10.9 (2.6)	-0.9	4.1	65	-11.5 (2.4)	-1.4	3.4	53	2.9 (2.6)	12.9	7.8
3	3	57	-1.6 (2.3)	57	-5.7 (2.3)	-4.1	0.3	65	-5.6 (2.1)	-4	0.3	53	10.9 (2.3)	12.5	8
3	4	57	-0.3 (2.4)	55	-0.2 (2.5)	0.1	4.9	64	-4.1 (2.3)	-3.7	0.9	53	16.2 (2.5)	16.5	11.7
3	6	57	-7.6 (2.3)	57	-10.2 (2.3)	-2.6	1.9	63	-9.3 (2.2)	-1.7	2.6	53	5.1 (2.4)	12.7	8.2
3	8	55	-5.6 (2.6)	57	-9.4 (2.5)	-3.8	1.2	62	-13.5 (2.4)	-7.9	-3	52	1 (2.6)	6.6	1.5
3	10	55	-5 (2.3)	57	-4 (2.2)	1.1	5.4	62	-8 (2.1)	-3	1.3	52	7.9 (2.3)	13	8.5
3	12	56	-10.4 (2.4)	56	-11.4 (2.4)	-1	3.7	62	-12.5 (2.3)	-2.1	2.5	52	-3.5 (2.5)	6.9	2.1
3	14	56	-5.6 (2.2)	57	-8.5 (2.2)	-2.9	1.5	61	-9.6 (2.2)	-3.9	0.4	51	1.1 (2.4)	6.8	2.3
3	16	56	-2.8 (2.3)	56	-7.1 (2.3)	-4.3	0.2	60	-10.4 (2.2)	-7.6	-3.2	52	2.2 (2.4)	5	0.5
3	18	55	-2.3 (1.9)	55	-5 (1.9)	-2.6	1	59	-9.1 (1.8)	-6.8	-3.2	53	8.1 (1.9)	10.5	6.8
6	1	55	-3.5 (2.1)	57	-9.8 (2.1)	-6.3	-2.2	55	-10.9 (2.1)	-7.4	-3.3		N/A	N/A	N/A
6	2	54	2.1 (2.2)	57	-6.2 (2.1)	-8.4	-4.2	55	-5 (2.2)	-7.1	-2.9		N/A	N/A	N/A
6	3	53	-3 (2.5)	57	-2.1 (2.4)	0.8	5.6	55	-8.3 (2.4)	-5.4	-0.6		N/A	N/A	N/A
6	4	53	-4 (2.2)	55	-2.1 (2.2)	1.8	6	54	-7 (2.2)	-3.1	1.2		N/A	N/A	N/A
6	6	54	-9 (2.7)	57	-11.2 (2.6)	-2.2	3	55	-12 (2.7)	-2.9	2.3		N/A	N/A	N/A
6	8	54	-9.3 (2.5)	57	-10.4 (2.5)	-1.1	3.7	55	-11.8 (2.5)	-2.4	2.5		N/A	N/A	N/A
6	10	54	-0.5 (2.5)	56	-4.6 (2.4)	-4.1	0.7	54	-7.9 (2.5)	-7.4	-2.5		N/A	N/A	N/A
6	12	54	-8.9 (2.5)	55	-9.2 (2.5)	-0.2	4.6	54	-11.2 (2.5)	-2.2	2.6		N/A	N/A	N/A
6	14	54	-1.3 (2.2)	56	-3.7 (2.2)	-2.4	1.9	52	-5.7 (2.3)	-4.3	0		N/A	N/A	N/A
6	16	55	-13.8 (2.2)	56	-17 (2.2)	-3.3	1.1	53	-17.7 (2.3)	-3.9	0.4		N/A	N/A	N/A
6	18	55	-3 (2.2)	56	-3.6 (2.1)	-0.6	3.6	52	-9.2 (2.2)	-6.2	-1.9		N/A	N/A	N/A
6	23.75	53	1.4 (2.8)	52	-3 (2.8)	-4.4	1.1	52	-4.7 (2.8)	-6.1	-0.6		N/A	N/A	N/A

For the categorical analysis the sponsor reported that in the PDS set the percentage of subjects with new onset values for QTcI of ≥ 450ms was 7, 5, 2, and 15 in the placebo, 400 mg/day lacosamide, 800 mg/day lacosamide, and moxifloxacin groups, respectively. In the all randomized set this reviewer found that there were 3 additional subjects with QTcI ≥ 450 ms in the lacosamide 800 group. In this set the percentages were 6, 5, 6, and 17 in the placebo, 400 mg/day lacosamide, 800 mg/day lacosamide, and moxifloxacin groups, respectively.

In the PDS set the percentage of subjects with increases in QTcI that were 30 to 60 ms was higher in the moxifloxacin group and placebo groups, 54% and 37%, respectively, compared with 27% and 19% in the 400mg/day and 800mg/day lacosamide groups, respectively. In the all randomized set the percentages with QTcI increases between 30 and 60 ms were 32, 25, 19, and 56, in the placebo, 400 mg/day lacosamide M, 800 mg/day lacosamide, and moxifloxacin groups, respectively.

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

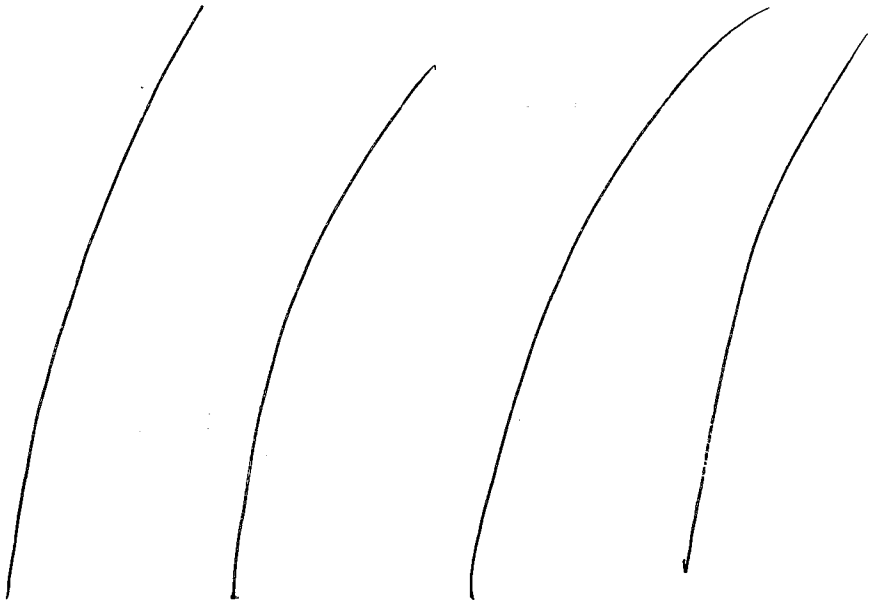
Reviewer's comments: The scheduled plasma concentrations measurements on Day 5 (morning and evening pre-dose) were not provided for the analysis. Furthermore, there were 11 female replacements for dropouts in the supratherapeutic treatment group and no male replacements.

5.2.1 QTc Corrections

The observed QT-RR interval relationship is presented in Figure 7 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI) methods.

Both the QTcF and QTcI are reasonable QT correction methods removing the heart rate effect illustrated by a horizontal trend in the QT vs. RR relationship. Thus, the QTcI correction method was used for the concentration QTc analysis to be comparable with the sponsor's analysis.

Figure 7: Baseline day QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).



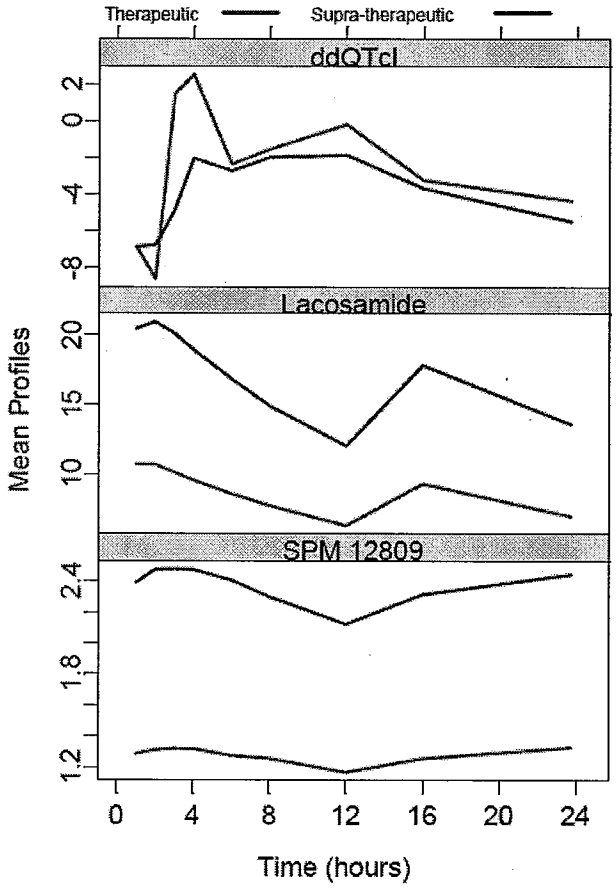
b(4)

5.2.2 ΔΔQTcI and Concentration Time Profiles

The ΔΔQTcI (baseline and placebo corrected QTcI) versus lacosamide and the main metabolite SPM12809 concentration is plotted in 8. The largest ΔΔQTcI of approximately -8 msec change was observed at the time to the peak of lacosamide and SPM12809 concentration (t_{max}).

APPEARS THIS WAY
ON ORIGINAL

Figure 8: Mean ΔΔQTcI, Lacosamide, and SPM12809 concentrations vs. Time for therapeutic dose of 400 mg/day (blue line) and supra-therapeutic dose of 800 mg/day (red line).



5.2.3 Exposure-Response Modeling

The relationship between ΔΔQTcI and concentrations of lacosamide and the main metabolite SPM12809 was investigated by using a linear mixed-effects model. Data collected from the two dose groups (400 mg/day and 800 mg/day) were pooled for the analysis.

Both lacosamide and the main metabolite SPM12809 were found to shorten the QTc interval. Table 10 and Table 11 summarize the results of the lacosamide and SPM12809 concentration-QTcI analyses. No statistical significant intercept was identified and model 2 was applied for both the lacosamide and the metabolite analysis.

Table 10: Exposure-Response Analysis of Lacosamide associated ΔΔQTcI Prolongation

	Estimate (90% CI); p-value
Model 1: ΔΔQTcI = Intercept + slope*log(Lacosamide conc)	
Intercept, ms	4.17 (-1.55, 9.89) 0.23
Slope, ms per µg/mL	-2.93 (-5.19, -0.67) 0.03
Residual Variability, ms	14.2
Model 2: ΔΔQTcI = Intercept + slope*log(Lacosamide conc) (Fixed Intercept)	
Intercept, ms	0
Slope, ms per µg /mL	-1.33 (-1.88, -0.78) 0.0001
Residual Variability, msec	14.2
Model 3: ΔΔQTcI = slope*log(Lacosamide conc) (No Intercept)	
Slope, ms per µg /mL	-1.26 (-1.82, -0.70) 0.0003
Residual Variability, ms	14.3

Table 11: Exposure-Response Analysis of SPM12809 associated ΔΔQTcI Prolongation

	Estimate (90% CI); p-value
Model 1: ΔΔQTcI = Intercept + slope*log(SPM 12809 conc)	
Intercept, ms	-1.21 (-2.78, 0.35) 0.20
Slope, ms per µg/mL	-4.27 (-6.56, -1.98) 0.003
Residual Variability, msec	14.2
Model 2: ΔΔQTcI = Intercept + slope*log(SPM 12809 conc) (Fixed Intercept)	
Intercept, ms	0
Slope, ms per µg/mL	-5.08 (-7.11, -3.05) <0.0001
Residual Variability, msec	14.2
Model 3: ΔΔQTcI = slope*log(SPM 12809 conc) (No Intercept)	
Slope, ms per µg/mL	-5.64 (-7.70, -3.58) <0.0001
Residual Variability, ms	15.0

Based on model 2 for both lacosamide and SPM12809, the predicted ΔΔQTcI interval at the mean peak lacosamide and SPM12809 concentrations after steady-state dosing of the

proposed therapeutic (400 mg/day) and supra-therapeutic (800 mg/day) doses are presented in Table 12 and Table 13.

Table 12: Predicted Change of ΔΔQTcI Interval at Steady State Peak Lacosamide Concentration

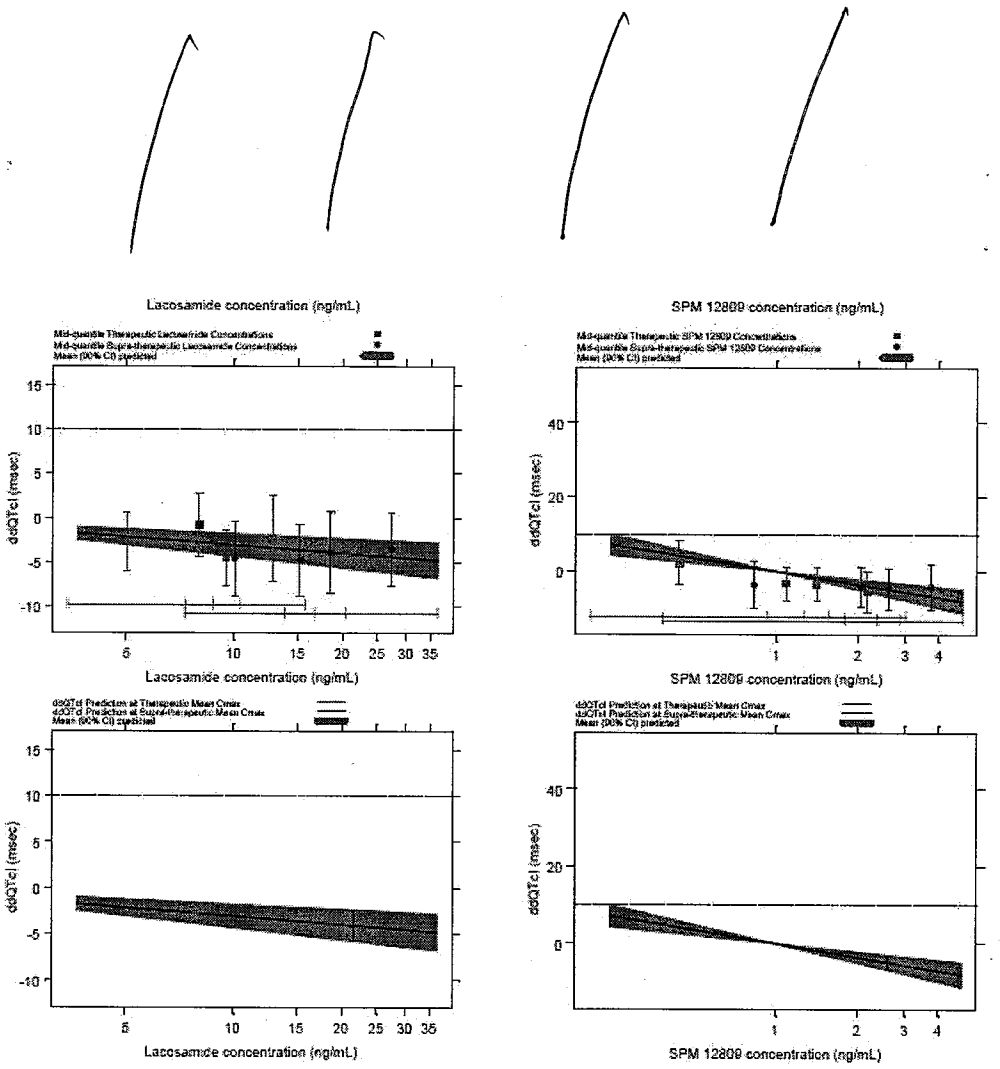
Dose Group	Predicted change in ΔΔQTcI interval (ms)	
	Mean	90% Confidence Interval
400 mg/day (steady-state)		
Mean C_{max} (11.1 ng/ml)	-3.20	(-4.52, -1.88)
800 mg/day (steady-state)		
Mean C_{max} (21.7 ng/ml)	-4.09	(-5.78, -2.40)

Table 13: Predicted Change of ΔΔQTcI Interval at Steady State Peak SPM12809 Concentration

Dose Group	Predicted change in ΔΔQTcI interval (ms)	
	Mean	90% Confidence Interval
400 mg/day (steady-state)		
Mean C_{max} (1.40 ng/ml)	-1.71	(-2.39, -1.03)
800 mg/day (steady-state)		
Mean C_{max} (2.61 ng/ml)	-4.88	(-6.83, -2.93)

The relationship between lacosamide and SPM 12809 concentrations and ΔΔQTcI are visualized in Figure 9. The raw ΔΔQTcI vs. lacosamide and SPM12809 concentration are shown in Figure 9 top left and right graphs. The goodness-of-fit is illustrated in the middle left and right graph of Figure 9 showing the observed mid-quartile concentrations and associated mean ΔΔQTcI (90% CI) reasonably within the mean (90% CI) predicted ΔΔQTcI (black line with shaded grey area). The mean (90% CI) predicted ΔΔQTcI at mean C_{max} after steady-state dosing of therapeutic dose (400 mg/day) and supra-therapeutic dose (800 mg/day) are shown in the bottom left and right graphs of Figure 9.

Figure 9. (Top) ΔΔQTcI vs. lacosamide (Left) and SPM12809 (Right) plasma concentration. (Middle) Mean (90% CI) predicted ΔΔQTcI vs. lacosamide plasma concentration (black line with shaded grey area) with the observed mid-quartile concentrations and associated mean (90%CI) ΔΔQTcI overlaid for therapeutic (blue) and supra-therapeutic (red) doses. (Bottom) Predicted ΔΔQTcI at mean C_{max} after steady-state dosing of therapeutic dose (400 mg/day, blue line) and supra-therapeutic dose (800 mg/day, red line)



b(4)

5.3 CLINICAL ASSESSMENTS

None of the adverse events identified as significant in the ICH E14 guidelines (i.e., sudden death, torsade de pointes, ventricular tachycardia, syncope, and seizures) were observed during the trial.

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

Procedure schedule for lacosamide 400mg/day and placebo dose groups

Trial Phase	EA	Baseline (Check-in to site)	Treatment Phase	Treatment Phase	Treatment Phase	Discharge	Safety Follow-Up
Day	-28 through Day-3	-2/-1[a]	1	2-5	6	7	At least 14 days
Obtain informed consent	X						
Inclusion/Exclusion criteria	X	X					
Serology	X						
Serum pregnancy test (female subjects)	X	X					X
Prior/concomitant medication assessment	X	X	X	X	X	X	X
Medical history	X						
Physical examination	X	X[b]				X[b]	X
Safety ECGs at site	X	X[b]	X[c]	X[c] (Day 3 only)	X[c]		X
Vital sign measurements	X	X[c]	X[c]	X[c]	X[c]	X	X
12-lead ECG from H-12 (flash card placed in AM of Days-1, 1, 3, 6)		X[d]	X[d]	X[d] (Day 3 only)	X[d]		
Safety laboratory (blood + urine)	X	X				X[b]	X
Alcohol and drug test	X	X					
Randomization		X					
Administration of trial medication (see Section 5)			LCM 200mg bid/ placebo	LCM 200mg bid/ placebo	LCM 200mg bid/ placebo		
PK blood samples				X[e]	X[e]		
Inquiry of well being/assessment of AEs							▶X

[a] Subjects are admitted in the evening of Day -2. All baseline assessments are completed upon admission except for 12-lead ECG from H-12, vital signs and safety ECG.
[b] Brief
[c] At 2-3 hours after morning dose (or flashcard placement on Day -1). Vital signs includes orthostatic assessment on Day -1, 4, and 6.
[d] ECGs 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 hours on Days -1, 1, 3, and 6 in triplicate (3 ECGs within 1 minute of the time point). Times are relative to morning dose on Days 1 and 3 and at the same respective time during the day on Day -1.

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

/s/

Stephen Grant
7/25/2007 12:00:36 PM
MEDICAL OFFICER

Christine Garnett
7/25/2007 12:26:47 PM
PHARMACOLOGIST
Christoffer Tornoe was the clinical pharamcology reviewer.

Joanne Zhang
7/25/2007 01:22:08 PM
BIOMETRICS

Tristan Massie
7/25/2007 01:27:12 PM
BIOMETRICS

Norman Stockbridge
7/25/2007 02:56:42 PM
MEDICAL OFFICER

4.4 OCP Filing and Review Form

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Numbers	22-253, 22-254. —— (DAARP)	Brand Name	No proposed trade name b(4)
OCP Division (1, 2, 3, 4, 5)	DCP 2	Generic Name	Lacosamide
Medical Divisions	DAARP	Drug Class	
OCP Reviewer	Emmanuel O Fadiran	Indication(s)	• Diabetic Peripheral Neuropathic (DPN) • Partial onset seizures
OCP Team Leader	Suresh Doddapeneni	Dosage Forms/Strength	• Film-coated tablets – 50, 100, 150, 200, 250, 300 mg • —— • Injection – 10 mg/ ml b(4)
		Dosing Regimen	
Date of Submission	09/28/2007	Route of Administration	Oral /IV
Estimated Due Date of OCP Review	05/26/2008	Sponsor	Schwarz Biosciences, Inc
PDUFA Due Date	07/28/2008	Priority Classification	S
Division Due Date	05/26/2008	Submission Type	NME

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	6	6	
Blood/plasma ratio:	x	1	1	
Plasma protein binding:	x	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3	3	
multiple dose:	x	2	2	

Patients-				
single dose:	x	2		
multiple dose:	x	2		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:	x	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3		
In-vivo effects of primary drug:	x	6		
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1	1	
gender:	x	1	1	
pediatrics:	x			Request for deferral for studies in pediatric patients below — years. b(4)
geriatrics:	x	(1)	(1)	
renal impairment:	x	1	1	
hepatic impairment:	x	1	1	
PD:				
Phase 2:	x	3	3	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			
Phase 3 clinical trial:	x			
Population Analyses -				
Data rich:	x	2	2	
Data sparse:	x	3	3	
II. Biopharmaceutics				
Absolute bioavailability:	x	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	3	3	
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS	x			
BCS class	x			BCS 1
III. Other CPB Studies				
Genotype/phenotype studies:	x	1	1	
Abuse potential	x	1		Consult to CCS
Pediatric development plan				
QTc	x	1	1	Review was conducted by QT IRT under IND 57, 939.
Total Number of Studies		33		
Filability and QBR comments				
	"X" if yes	Comments		

Application filable?	x	• See below.
Comments sent to firm?		1. Please submit the applicable data from the following to support the population PK analyses and concentration-response relationship analyses: •All datasets used for model development and validation should be subm as SAS transport files (*.xpt). A description of each data item shoul provided in a Define.pdf file. Any concentrations and/or subjects that h been excluded from the analysis should be flagged and maintained in datasets. •Model codes or control streams and output listings should be provided all major model building steps, e.g., base structural model, covariates mo final model, and validation model. These files should be submitted as AS text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). •A model development decision tree and/or table which gives an overvie modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results. 2. Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given. 3. The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.
QBR questions (key issues to be considered)	• Is the metabolism (*in vitro and in vivo)* of lacosamide well characterized? • Are appropriate drug-drug interaction studies conducted? • Is there an E-R relationship for DNP? • Are there important covariates that affect PK of lacosamide? • Are there exposure data in special populations for labeling? • Are the information on the PK and E-R in the labeling appropriate?	

APPEARS THIS WAY
ON ORIGINAL

b(4)

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

/s/

Lei K Zhang
6/11/2008 10:39:43 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/11/2008 03:27:31 PM
BIOPHARMACEUTICS
I concur.

Suresh Doddapaneni
6/11/2008 05:59:01 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Lacosamide
PRODUCT (Brand Name):	VIMPAT
NDA:	22-253, 22-254 b(4)
DOSAGE FORM:	Tablets b(4) and Solution for Injection b(4)
DOSAGE STRENGTHS:	Tablets: 50, 100, 150, 200, 250 and 300 mg Solution for Injection: 10 mg/mL b(4)
INDICATION:	Treatment of Partial Seizures
NDA TYPE:	1S
SUBMISSION DATES:	9/28/07, 11/26/07, 12/13/07
SPONSOR:	Schwartz Pharma
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
PHARMACOMETRICS REVIEWER	Hao Zhu, Ph.D.
PHARMACOMETRICS TEAM LEADER	Joga Gobburu, Ph.D
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY 5
1.1 RECOMMENDATION 5
1.2 PHASE IV COMMITMENT 5
1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS 6

2.0 QUESTION BASED REVIEW 14

2.1 GENERAL ATTRIBUTES 14
2.1.1 Drug/Drug Product Information: 14

2.2 GENERAL CLINICAL PHARMACOLOGY 18
2.2.1 What are the clinical studies used to support dosing or claims for epilepsy and what are their design features? 18
2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies? 20
2.2.3 What are the characteristics of exposure/effectiveness relationships? 21
2.2.4 Are the proposed dosage regimens for partial seizures indications adequately supported by the clinical trial and consistent with the dose-respons relationship? 23
2.2.5 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?
2.2.6 What are the ADME characteristics of Lacosamide? 23
2.2.7 What are the basic pharmacokinetic parameters of lacosamide after single and multiple doses? 27
2.2.8 Do the pharmacokinetic parameters change with time following chronic dosing? 29
2.2.9 What is the variability in the PK data? 30
2.2.10 How do the pharmacokinetics of the drug in healthy volunteers compare to that in epilepsy patients? 30
2.2.11 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship? 32

2.3 INTRINSIC FACTORS 34
2.3.1.1 Effect of Renal Impairment: 34
2.3.1. 2 Effect of Hepatic Impairment: 37
2.3.1. 3 Effect of age: 39
2.3.1.4 Effect of Gender: 40
2.3.1.5 Effect of Race: 41
2.3.1.6 Effect of CYP2C19 polymorphism 26

2.4 EXTRINSIC FACTORS 43
2.4.1 Is lacosamide a substrate, inhibitor or inducer of CYP enzymes? 43
2.4.2 Is lacosamide a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system? 43
2.4.3 Is there an in vitro basis to suspect drug-drug interaction? 43
2.4.4 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment? 44
2.4.4.1 Influence of lacosamide on other drugs: 44
2.4.4.2 Influence of lacosamide on concomitant AEDs exposure: 45
2.4.4.3 Influence of AEDs on lacosamide exposure: 45

2.5 GENERAL BIOPHARMACEUTICS 46
2.5.1 What the relative bioavailability of the formulations (— solution

for injection) proposed for marketing and can they be used interchangeably? 46
2.5.2 Does the pharmacokinetics of lacosamide differ when switched from oral to iv dosing? 52
2.5.3 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification? 55
2.5.4. Is the proposed to-be-marketed formulation of lacosamide bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies? . 55

2.6 ANALYTICAL 59

4.1 APPENDIX I 92

4.1.1 INDIVIDUAL STUDY REVIEW 92

[redacted] 93

BE BETWEEN TABLETS AND SOLUTION FOR INFUSION 100
Study SP645: Randomized, open-label, single-dose, 2-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in healthy male subjects 100
Study SP658: Randomized, open-label, single-dose, 3-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in 24 healthy male subjects 105

REPLACEMENT OF ORAL WITH SOLUTION FOR INFUSION 112
Study SP757: A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization 112
Study SP616: A multicenter, double-blind, double-dummy, randomized trial to investigate the safety, tolerability and pharmacokinetics of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization 124

METABOLIC DIFFERENCES BETWEEN ORAL AND IV DOSING 131
Study SP643: Randomized, open-label, 2-way crossover trial to investigate the... 131 pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (CYP2C19) 131

OTHER 138
Study SP834: Randomized, double-blind, placebo controlled, parallel group, single intravenous ascending dose study to determine the tolerability and pharmacokinetic profile of ADD 234037 (first in human study) 138

DRUG-DRUG INTERACTIONS WITH ANTIEPILEPTICS 142
Study SP601: Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of SPM 927 (harkoseride) on valproic acid (VPA) in 16 healthy male Caucasian volunteers 142
Study SP602: Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of valproic acid (VPA) on SPM 927 (harkoseride) in 16 healthy male Caucasian volunteers 147
Study SP618: Open-label multiple dose study to evaluate the effect of SPM 927 (harkoseride) on the pharmacokinetics of carbamazepine (CBZ) in 20 healthy male Caucasian volunteers 153
Study SP603: Open-label multiple dose study to evaluate the effect of carbamazepine (CBZ) on the pharmacokinetics SPM 927 (harkoseride)in 20 healthy male Caucasian volunteers 161

APPENDIX II 168

OCPB FILING REVIEW 168

1.0 EXECUTIVE SUMMARY

b(4)

Lacosamide is a new molecular entity that is proposed to be marketed in — dosage forms: as tablets (NDA 22-253), solution for infusion (NDA 22-254) —

The proposed indications for lacosamide are for adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy aged 16 years and older (tablet, solution for infusion, — and for the management of neuropathic pain associated with diabetic peripheral neuropathy (tablet only). b(4)

NDA 22-253, NDA 22-254 — are for indication of partial seizures and that for the indication of neuropathic pain is NDA — b(4)

b(4)

The sponsor proposed dosing regimen for — indications is 200— mg per day of lacosamide as maintenance dose, administered in two equally divided doses. Doses are proposed to be titrated once a week starting from 100 mg/day.

The precise mechanism of action by which lacosamide exerts its antiepileptic and analgesic effects in humans is not fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing while exerting no effects on physiological neuronal excitability.

Synonymous terms for lacosamide throughout this review is: Lacosamide, LCM; SPM 927; harkoseride.

This review only focused on the epilepsy indication and dosage forms (solution for infusion — in addition to the tablets) used for epilepsy. The drug interaction studies specific to the epilepsy indication is also part of this review. The general pharmacokinetics of the LCM, special population studies and drug interaction studies are reviewed by Drs. Tayo Fadiran and Lei Zhang from the Division of Clinical Pharmacology 2 (DCP-2) supporting Division of Analgesics, Anesthetics and Rheumatology Products (DAARP). The pharmacometrics review including population pharmacokinetics in healthy subjects as well as partial seizures patients and exposure response analysis in partial seizures patients is reviewed by Dr. Hao Zhu from the Pharmacometrics Group. b(4)

This review abstracts the relevant information from Dr. Zhang and Hao's review and summarizes it the Overall summary of Findings. The respective reviews should be referred to for details on the topic reviewed by them.

1.1 RECOMMENDATION

b(4)

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to NDAs 22-253, 22-254 — on September 28, 2007 and finds it acceptable pending DSI inspection and provided that a

mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 PHASE IV COMMITMENTS

The following Phase IV commitments are taken from Dr. Zhang's review.

To better understand drug interaction potential for lacosamide, the Sponsor is recommended to provide the following data as a Phase 4 commitment:

- Determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

All clinical pharmacology information related to the partial epilepsy indication (including the solution for infusion — dosage forms and relevant drug interactions) is reviewed and summarized in this review. The general pharmacokinetics of lacosamide is reviewed by Drs. Fadiran and Zhang, but relevant information is taken from their review and repeated here to aid the readers in understanding the overall findings of the Clinical Pharmacology of LCM. Similarly the Findings from the Pharmacometrics review by Dr. Zhu is also summarized here. b(4)

The initial summary section summarized the overall findings for the epilepsy indication.

Exposure-Response for Effectiveness in patient with Partial Seizures: (This is taken from Dr. Zhu's review)
The exposure-response relationship for lacosamide in treating patients with partial seizure is established in the responder patient population based on clinical observations in 3 clinical effectiveness studies (SP667, SP754, and SP755). The exposure is defined as area under the curve (AUC) over a dosing interval of 12 hours at steady state. The response is defined as change from baseline of the average daily number of partial seizure.
Based on efficacy ER analysis, 600 mg does not provide additional efficacy compared to 400 mg.

b(4)

b(4)

Bioequivalence between the Solution for Infusion and Oral Tablets:
The sponsor has conducted two BE studies in healthy subjects evaluating the bioequivalence of solution for infusion at different infusion rates versus the oral tablets (Study SP645 and SP658)
The following observations were made from the bioequivalence studies using infusion times of 15, 30 and 60 minutes:

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

The 90% confidence intervals for the pharmacokinetic parameters from these studies are given below:

ANOVA results for the comparison "LCM as solution for infusion"/"LCM as tablet" – SP645 and SP658

Trial	Drug Formulation	Parameter	Point Estimate	90% Confidence Interval
SP645	Solution for infusion (15 min) /tablet	AUC(0-tz)	0.98	(0.96, 1.01)
		Cmax	1.20	(1.04, 1.38)
SP658	Solution for infusion 30 min)/tablet	AUC(0-tz)	1.00	(0.98, 1.01)
		Cmax	1.15	(1.07, 1.22)
	Solution for infusion (60 min)/tablet	AUC(0-tz)	1.00	(0.98, 1.02)
		Cmax	1.03	(0.96, 1.10)

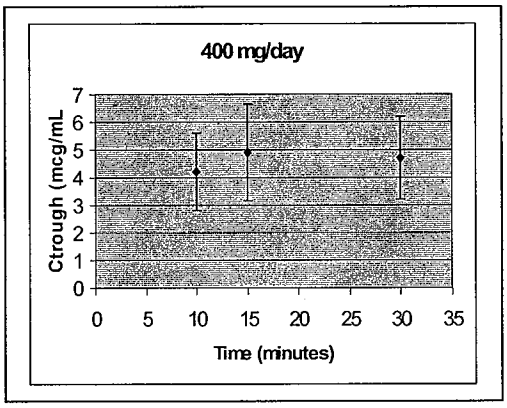
The Medical Officer is evaluating the adverse events at the three different infusion rates. Additional information of different infusion rates is given below.

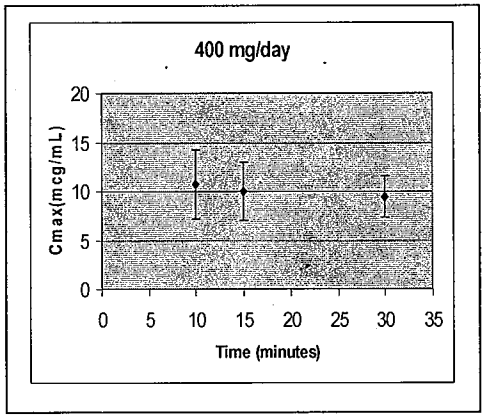
Replacement of Oral Tablets with IV solution in patients:
In addition to these bioequivalence studies the sponsor also evaluated the safety and tolerability of various infusion durations in patients with concomitant AEDs in two clinical studies SP757 and SP616. In study SP757 subjects were on stable 200-800 mg/day oral doses of lacosamide and were switched to the same iv dose for 2-5 days. Study SP616 was a crossover replacement study. The number of subjects in the different infusion groups were:

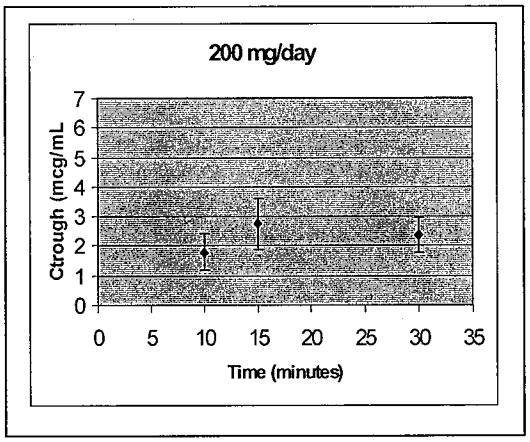
Sample size from the clinical studies:

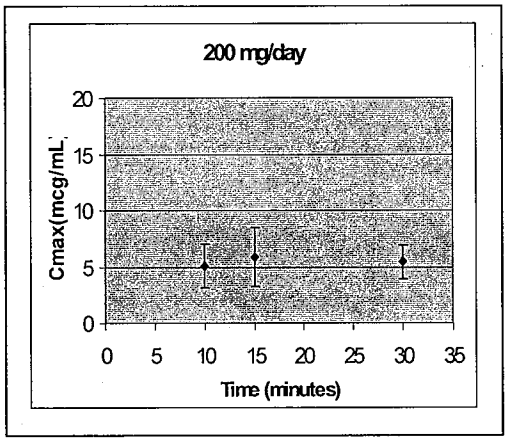
Infusion Duration	Study 757	Study 616
10 minutes	N=20	-
15 minutes	N=100	-
30 minutes	N=40	N=30
60 minutes	-	N=30

Minimal differences in the Ctrough and Cmax values for the 10, 15 and 30 minute infusion durations were seen from Study SP757 as seen in the following figures.









It can be concluded from these figures that the 10, 15 and 30 minute infusions at a given dose give comparable plasma concentrations of LCM.

When comparing to the C_{trough} of the oral tablets from Study SP757, the ratio of geometric means were 85-95%, indicating that normalized C_{trough} plasma concentrations following iv LCM administration were comparable to normalized C_{trough} plasma concentrations after oral LCM administration. The geometric mean ratios iv/oral for the $C_{min,norm}$ from Study SP616 was also approximately 89-93%, suggesting that the Cmins slightly decrease after iv administration.

In study SP616, the Values of $C_{max,norm}$ were slightly elevated after iv treatment (30 and 60 minute) compared to oral treatment. This is reflected in ratios iv/oral of 111-118% for $C_{max,norm}$. These values are similar to that seen with the definitive bioequivalence study with the 15 minute infusion. These higher concentrations were seen within the first 1.75 hours of dosing.

Therefore from a pharmacokinetic standpoint, although the definitive bioequivalence study showed that the 15 minute infusion showed a 20% higher Cmax compared to the oral LCM and failed the bioequivalence limit, the clinical relevance of this on the overall steady state concentrations may be minimal. The safety aspects at different infusion rates are being reviewed by the Safety reviewer.

Pharmacokinetic Differences in Healthy Subjects and Patients with Partial Seizures:
The LCM plasma concentrations showed dose proportionality in the patient population as well as inhealthy subjects. The trough concentrations of LCM in the partial seizure populations were comparable to those observed in healthy subjects at steady state.

Drug-Drug Interactions with Antiepileptics:
In these studies lacosamide doses used were 200 mg BID (400 mg/day)

Effect of 400 mg/day lacosamide on pharmacokinetics of AEDS:

Drug	Effect (Traditional PK)	Effect (POP PK)
Carbamazepine, 200 mg BID	None	Not evaluated
Valproic acid, 300 mg BID	None	Not evaluated

Effect of AEDs on 400 mg/day lacosamide pharmacokinetics:

Drug	Effect (Traditional PK)	Effect (POP PK)
Carbamazepine, 200 mg BID	None	15-20% ↓
Valproic acid, 200 mg BID	None	none
Phenytoin	Not evaluated	15-20% ↓
Phenobarbital	Not evaluated	15-20% ↓

The drug-drug interaction covariate effects from population PK analysis are difficult to interpret. In population PK analysis using data from patients with partial onset seizures, the sponsor did not demonstrate statistical significance when using coadministration of carbamazepine alone as a covariate. About 80% (55 out of 69) patients in SP754 study who took carbamazepine concurrently took 1 or 2 other medications (topiramate, lamotrigine, valproate, levetiracetam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, gabapentin). Given this, it is unclear whether the significant covariate effect is driven by carbamazepine or some other drugs. Based on the relatively small effect seen, no dosage adjustment is necessary when taking concomitant AEDs.

The findings from overall clinical pharmacology and biopharmaceutics sections as reviewed by Dr. Fadiran and Zhang are as follows:

Twenty-five Phase 1 trials investigated the clinical pharmacology of LCM. Overall, 788 healthy subjects, 8 subjects with hepatic impairment, 32 subjects with renal impairment were enrolled in these studies. Of these, 683 subjects were treated with LCM.

General Pharmacokinetics (ADME characteristics) of Lacosamide (This has been taken from the review of Drs Fadiran and Zhang):

Absorption: Following oral administration, lacosamide is absorbed with a Tmax of approximately 0.5 to 4 hours after dosing. Absolute bioavailability of lacosamide was determined to be ~100% indicating an almost complete absorption of LCM after oral administration.

Distribution: After IV administration as well as after oral administration, the V_d of LCM was between approximately 40 and 60L, indicating that LCM is distributed in the total body water. Less than 15% of LCM is bound to plasma proteins.

Metabolism: In vitro incubation with human liver microsomes, hepatocytes, kidney microsomes, and plasma showed a low metabolic turnover of LCM (<4% at 4 hours). Two metabolites, SPM 12809 (desmethyl) and SPM 6912 (desacetyl) were found in trace (<3%). However, the human radiolabeled ADME study (SP619) suggested that lacosamide was metabolized in vivo. Only 40% of unchanged LCM was recovered in urine and about 30% of the dose was recovered in urine as SPM 12809, the major metabolite. Another 20% of dose was polar fraction (structure unidentified). SPM 12809 is not pharmacologically active. Levels of SPM 12809 in plasma and urine were confirmed in several PK studies. SPM 12809 represents approximately 10% of the parent compound in plasma.

The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. The Sponsor determined that lacosamide is a CYP2C19 substrate and formation of SPM 12809 is via this pathway. The Sponsor did not study other CYP isoforms in the recombinant systems. The role of other enzymes in lacosamide metabolism is unknown.

Elimination: The elimination half-life of LCM is approximately 13 hours. The elimination half-life of SPM 12809 is between approximately 15 and 23 hours and is not altered by different doses or by multiple dosing.
Renal is major clearance pathway for lacosamide as 95% of dose was recovered in urine either as lacosamide (30-40%) or other metabolites.

Single dose and multiple dose pharmacokinetics: (This has been taken from the review of Drs Fadiran and Zhang)
Steady state plasma concentrations are achieved after 3 days of repeated administration (twice daily).

Dose proportionality: (This has been taken from the review of Drs Fadiran and Zhang)
Lacosamide is dose proportional in range of 100-800 mg after single doses.

Special Populations: (This has been taken from the review of Drs Fadiran and Zhang):

Renal Impairment: Systemic exposure of lacosamide (AUC) increased with increasing degree of renal impairment. Mean AUC increased 27%, 23%, and 59% in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function, respectively. . Renal clearance of lacosamide decreased with increasing degree of renal impairment. For C_{max}, only a slight difference was observed. The terminal half-life of lacosamide in plasma ($t_{1/2}$) was prolonged in subjects with severe renal impairment (approximately 18 hours) in comparison with normal renal function subjects (approximately 13 hours).

The plasma concentrations of the metabolite, SPM 12809, also increased with increasing degree of renal impairment. The increases were more profound than lacosamide. AUC increased 4-fold in patients with severe renal impairment compared to normal renal function subjects.

Subjects with endstage renal disease (ESRD) receiving hemodialysis showed that under a 4-hour dialysis starting 2.5 hours after dosing, $AUC_{(0-tz)}$ of LCM and SPM 12809 was approximately 50% lower in ESRD subjects receiving hemodialysis after a single oral dose of 100mg LCM compared with dosing on a dialysis-free day. C_{max} was less affected by dialysis than AUC, probably because the maximum plasma concentration was reached before the start of dialysis in most subjects.

Based on the results of this study, dose adjustment for patients with mild and moderate renal impairment may not be needed. However for patients with severe renal impairment, due to a mean 60% increase in AUC and highly variable data, the highest doses in severe renal impairment patients should be reduced to — of the highest doses recommended in patients who have normal renal function. b(4)

For patients with ESRD, due to the decreased plasma concentrations of lacosamide under dialysis conditions, dose adjustment has to be considered in clinical practice for patients under dialysis. An increased dose may be considered to reach the effective dose in these patients earlier. In addition, hemodialysis can be considered as an effective treatment to reduce lacosamide plasma concentrations, for instance in case of overdosing.

Hepatic Impairment: Plasma concentrations of lacosamide were approximately 50-60% higher in the subjects with moderate hepatic impairment (Child-Pugh Classification B) compared to subjects with normal hepatic function. Plasma concentrations of the main metabolite of lacosamide, SPM 12809, were approximately 40-50% lower in subjects with hepatic impairment compared to healthy subjects. The data indicate that hepatic metabolism is involved in the metabolism of lacosamide.

Similar to recommendation for severe renal impairment patients, the highest doses in moderate hepatic impairment patients should be reduced to — of the highest doses recommended in patients who have normal hepatic function. b(4)

PK of lacosamide has not been studied in mild or severe hepatic impairment patients. Caution should be exercised as metabolism of lacosamide is anticipated to be altered in these subjects.

Age:
Elderly: Exposure were higher in elderly male and female subjects compared with young male subjects. The elderly male subjects showed ~30% higher AUC than young male subjects. After taking weight into account, there was a 20-25% difference between elderly and young subjects. A 30% higher exposure in elderly may not warrant a dose adjustment based on age. However, caution should be exercised because elderly patients usually may also have impaired renal and hepatic function that lead to increased lacosamide exposure.

Pediatrics: The pharmacokinetic profile of lacosamide in pediatric patients has not been established.

Gender: The elderly female subjects showed ~15% higher AUC than elderly male subjects. When taking body weight differences into considerations, the difference between genders went away. No dosage adjustment is necessary.

Race: A slightly higher exposure (measured as $AUC_{\tau,ss}$) of LCM was observed in Asian and Black compared with White subjects (increase of approximately 10%). The body weight was slightly higher in the group of White subjects, and after normalization to body weight ($AUC_{\tau,ss,norm}$) the exposure for the 3 ethnic groups was similar.

With respect to SPM 12809, mean $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max,ss}$, $C_{max,ss,norm}$ as well as $A_{e(0-12)}$ of SPM 12809 were approximately 30% to 50% lower in Asian and Black subjects compared with White subjects. This difference is not considered clinically relevant because the exposure of SPM 12809 is lower in Blacks and Asians compared with White subjects and the metabolite of LCM has no known pharmacological activity.

No dose adjustment is needed based on race.

CYP2C19 Genotype: (This has been reviewed by Dr. Tandon)
Plasma concentrations of lacosamide were comparable (not more than 10% difference) between Poor Metabolizers (n=4) and Extensive Metabolizers (n=8) of CYP2C19, however, there were noticeable differences (75-80% difference) between PMs and EMs with respect to AUCs of the metabolite SPM 12809. PM and EM were classified based on genotype. PMs were homozygous for nonfunctional alleles and EMs were either heterozygous or homozygous for wild-type alleles. The data confirmed that CYP2C19 is involved in SPM 12809 formation. As level of SPM 12809 is low compared to lacosamide, dose adjustment based on CYP2C19 genotype is not needed.

Drug-drug Interactions: (Drug-Drug Interactions related to Epilepsy are reviewed by Dr. Tandon, the summary of other interaction studies are taken from reviews of Drs. Fadiran and Zhang). No dosage adjustment is necessary for any of the drug evaluated in drug interaction studies.

Effect of lacosamide on pharmacokinetics of other drugs:

Drug	Effect
Carbamazepine	None
Valproic acid	None
Digoxin	None
Oral Contraceptive	↑ Cmax of ethinylestradiol (~20%)
Omeprazole	None
Metformin	effect controversial, one group showed increase and the other group showed decrease in exposure of metformin. PD not studies. However, the magnitude of change on metformin PK is not considered clinically relavent.

Effect of other drugs on lacosamide pharmacokinetics:

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

Biopharmaceutics: (This has been taken from the review of Drs Fadiran and Zhang)

BCS Class: Lacosamide is a Biopharmaceutics Classification System (BCS) class 1 drug.
Bioequivalence: The to-be-marketed formulation is not studied in clinical trials. A biowaiver is requested based on BCS Class and is being reviewed by the Chemist
Food Effect: Food does not affect lacosamide PK. The highest strength was not used in the Food effect study.

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Ramana Uppoor, Ph.D._____

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths:

Tablets: Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets are colored, oval, ——— tablets of different size and are compositionally proportional formulations. Consequently, the size and weight increase with dosage strength. b(4)

b(4)

Solution for infusion: 10 mg/ml

Indication:

1. Partial Onset Seizures

Lacosamide tablets ——— are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older. b(4)

Lacosamide injection is an alternative for patients when oral administration is temporarily not feasible.

2. Neuropathic pain associated with Diabetic Peripheral Neuropathy

b(4)

Dosage and administration (Sponsor's Proposed):

Partial Onset Seizures:

Starting Dose: 50 mg BID (100 mg/day).
Increments: Weekly by 100 mg/day
Therapeutic Doses: 200 and 400 mg/day given as BID
Maximum Dose: ———

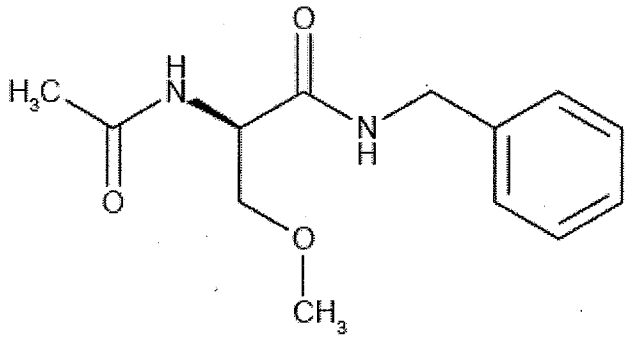
Doses can be given with or without food.

Replacement therapy with intravenous dose:
When switching from oral TRADENAME, the initial total daily intravenous dosage of TRADENAME should be equivalent to the total daily dosage and frequency of oral TRADENAME and should be infused intravenously over a period of ——— At the end of the intravenous treatment period, the patient may be switched to b(4)

TRADENAME oral administration at the equivalent daily dosage and frequency of the intravenous administration.

Pharmacologic Class: Sodium channel inactivator

Chemical Name. (R)-2-Acetamido-N-benzyl-3methoxypropionamide (IUPAC). Lacosamide is a functionalized amino acid. In this review the drug has been referred to by the following terms: Lacosamide, LCM; SPM 927; also previously referred to as harkoseride. Its molecular formula is C13H18N2O3 and its molecular weight is 250.30. The chemical structure is:



Physical Characteristics: Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol. It has a partition coefficient of Log $P_{octanol\text{-}water} = 0.25$. No pK_a within pH 1.5 – 12 was observed. Four crystalline forms and one amorphous form of lacosamide were identified. Except for the thermodynamically most stable form 1 and form 2, the other forms are not stable under normal conditions and are not formed / present in lacosamide drug substance.

Mechanism of action: A dual mode of action has been found for lacosamide through preclinical studies. It selectively enhances slow inactivation of voltage-gated sodium channels (VGSC) resulting in stabilization of hyperexcitable neuronal membranes. It is also found to interact with collapsin response mediator protein-2 (CRMP-2), a protein mainly expressed in the central nervous system (CNS) and involved in neuronal differentiation and axonal outgrowth.

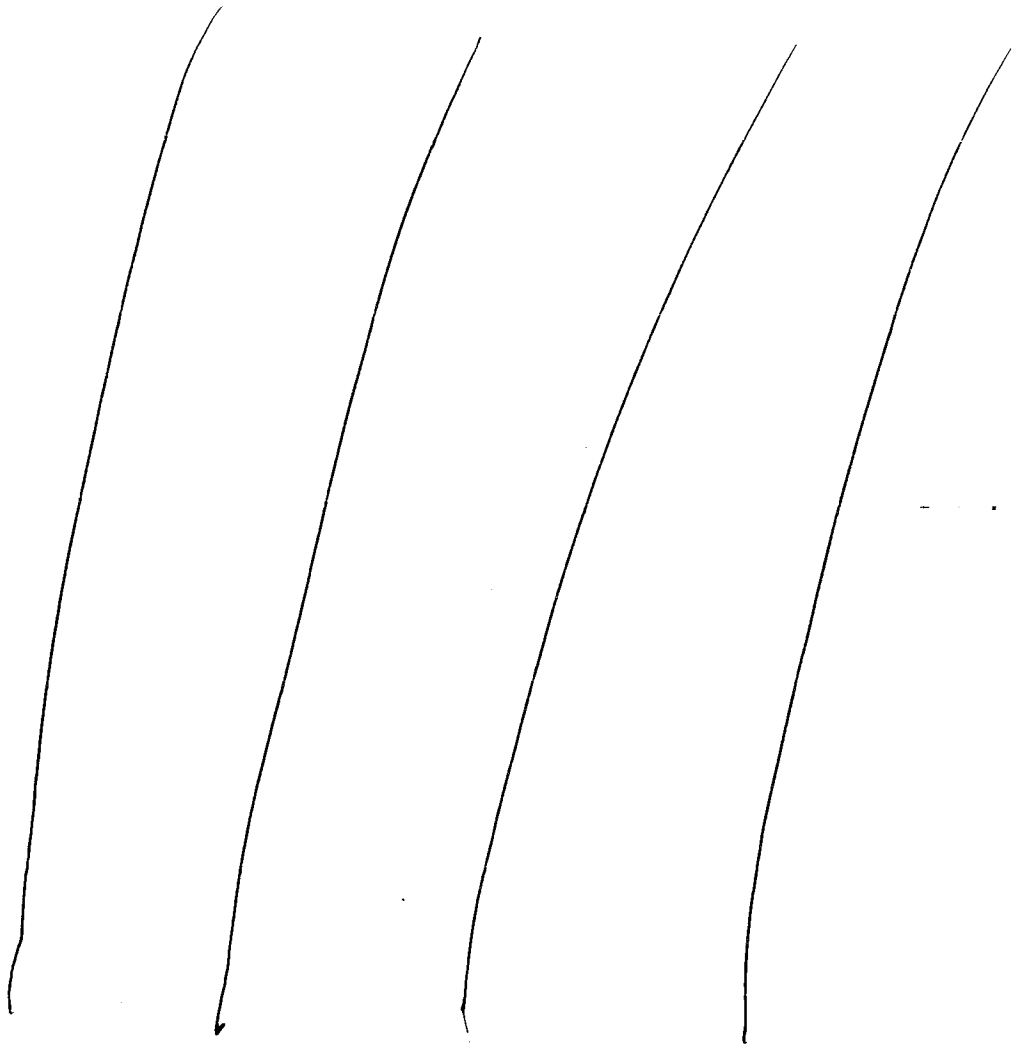
Formulation: Tablet:

Lacosamide Tablets are compositionally proportional formulations as seen in the Table below.

Quantitative composition per film-coated tablet

Component	Reference to standard	Function	50 mg pinkish [mg]	100 mg dark yellow [mg]	150 mg salmon [mg]	200 mg blue [mg]	250 mg [mg]	300 mg [mg]
Lacosamide	In-house	Active ingredient	50.00	100.00	150.00	200.00	250.00	300.00
Cellulose, microcrystalline	USP-NF							
Crospovidone	USP-NF							
Magnesium stearate	USP-NF							
Hydroxy-propylcellulose	USP-NF							
Total (film-coated tablet)			126.00	252.00	378.00	504.00		

b(4)



b(4)

Solution for injection: 10 mg/mL

Quantitative composition per mL of solution for infusion

Name of ingredients	Reference to standard	Function	Amount per mL
Lacosamide	In-house	Active ingredient	10.00 mg
Sodium chloride	USP	[redacted]	[redacted]
[redacted] hydrochloric acid	USP-NF	pH-adjustment	[redacted]
Water for injection	USP	[redacted]	[redacted]

b(4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims for epilepsy and what are their design features?

Tablets:

The clinical development program for LCM includes 7 clinical trials that evaluated efficacy of LCM as adjunctive oral (tablet) therapy in adult subjects with partial-onset seizures. This includes 3 primary double-blind, placebo-controlled efficacy trials (SP667, SP754, and SP755), 1 completed supporting trial (SP607), and 3 ongoing trials (SP615, SP756, and SP774) evaluating long-term efficacy.

Trials evaluating efficacy of oral (tablet formulation) LCM in adults with partial-onset seizures

Protocol number	Trial design	LCM dose	Maximum treatment duration	Total number of subjects[a]
Primary efficacy trials				**Randomized**
SP667	Multicenter, DB, PC	200, 400, and 600mg/day	21 weeks	418[b]
SP754	Multicenter, DB, PC	400 and 600mg/day	21 weeks	405
SP755	Multicenter, DB, PC	200 and 400mg/day	18 weeks	485
Supporting efficacy trial				**Treated with LCM**
SP607	Multicenter, OL, UC	Up to 600mg/day	14 weeks	91
Long-term efficacy trials				**Treated with LCM**
SP615	Multicenter, OL, UC	Up to 800mg/day	8 years	370
SP756	Multicenter, OL, UC	Up to 800mg/day	4 years	302
SP774	Multicenter, OL, UC	Up to 800mg/day	4 years	376
Other efficacy trials				**Treated with LCM**
SP586	Multicenter, OL, UC	Up to 600mg/day	4 weeks	13
SP598	Multicenter, OL, UC	Up to 600mg/day	20 months	8

DB=double-blind; LCM=lacosamide; OL=open-label; PC=placebo-controlled; UC=uncontrolled

The trials required forced up-titration to the target (randomized) dose over up to 6 weeks (SP667 and SP754) or 4 weeks (SP755). In all 3 trials, active treatment was initiated at 100mg/day and increased in weekly increments of 100mg/day to the target dose. The titration scheme used in these trials in given in the Table below:

Titration scheme used in randomized, controlled trials

	Titration Phase (up to 6 weeks)					
Randomized dose	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
LCM 600mg/day (SP667, SP754)	100mg/day	200mg/day	300mg/day	400mg/day	500mg/day	600mg/day
LCM 400mg/day						
SP667	Placebo	Placebo	100mg/day	200mg/day	300mg/day	400mg/day
SP754	100mg/day	200mg/day	300mg/day	400mg/day	400mg/day	400mg/day
SP755	100mg/day	200mg/day	300mg/day	400mg/day	NA	NA
LCM 200mg/day						
SP667	Placebo	Placebo	Placebo	Placebo	100mg/day	200mg/day
SP755	Placebo	Placebo	100mg/day	200mg/day	NA	NA
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

LCM=lacosamide; NA=not applicable
Note: A 1-step back-titration of 100mg/day or placebo was allowed in the case of intolerable adverse events at the end of the Titration Phase.

Solution for Infusion:

Two trials were conducted in subjects with partial-onset seizures using a solution for infusion of LCM, SP616 and SP757. These trials were designed to identify the appropriate infusion duration(s) for LCM as short-term replacement for oral LCM and to provide data to support the safety of that infusion rate.

SP616 enrolled subjects who were participating in the open-label extension trial SP615, and SP757 enrolled subjects who were participating in the open-label extension trials SP615, SP756, or SP774. At the end of SP616 and SP757, subjects had the opportunity to resume their participation with oral LCM in the open-label extension trial.

Trials of intravenously administered LCM in subjects with partial-onset seizures

Trial number/clinical development phase/trial design	Number of unique exposures to iv LCM[a]	Number of subjects exposed to iv placebo	Maximum duration of treatment
SP616/Phase 2/Multicenter, double-blind, double-dummy, randomized trial to investigate safety, tolerability, and PK of iv LCM as replacement for oral LCM[b]	30-min infusion: 19 60-min infusion: 20	30-min infusion: 11 60-min infusion: 10	2 days
SP757/Phase 3/Multicenter, open-label trial to evaluate safety and tolerability of iv LCM as a replacement for oral LCM	10-min infusion: 20 15-min infusion: 100 30-min infusion: 40	NA	2-5 days
Total[c]	10-min infusion: 20 15-min infusion: 100 30-min infusion: 59 60-min infusion: 20	30-min infusion: 11 60-min infusion: 10	NA

iv=intravenous; LCM=lacosamide; min=minute; NA=not applicable; PK=pharmacokinetics

a Subjects receiving LCM in SP616 and SP757 were previously exposed to oral LCM (200 to 800mg/day) in an open-label extension trial.

b Subjects receiving iv LCM received a placebo tablet and subjects receiving iv placebo received a LCM tablet.

c Total for the 30-min infusion rate represents subjects from SP616 and SP757.

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

Primary Endpoints:

Two primary variables were defined in each of these trials. For FDA, the primary variable was the change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase. For the European regulatory agencies, the primary variable was the response (improvement) to treatment of ≥50% from Baseline to the Maintenance Phase. All 3 trials were powered to be adequate and well-controlled trials for adjunctive therapy in adult subjects with partial-onset seizures including consideration of both primary variables.

Secondary Endpoints:
Some Secondary variables included:

- change in partial seizure frequency per 28 days from Baseline to Maintenance Phase (for European Union regulatory agencies)
- response to treatment of ≥50% from Baseline to Maintenance Phase (for FDA)

- response to treatment of ≥50%, ≥75% from Baseline to Treatment Phase (ie, Titration + Maintenance Phases)
- response to treatment of ≥25% to <50% or 50% to 75% from Baseline to Maintenance Phase (SP754 and SP755 only)
- Clinical Global Impression of Change at the end of the Titration (SP667 only) and Maintenance Phases
- Patient's Global Impression of Change at the end of the Maintenance Phase (SP754 and SP755 only)
- change in Seizure Severity Scale ratings from Baseline to the end of the Maintenance Phase (SP754 and SP755 only)
- change in Quality of Life in Epilepsy - 31 assessment from Baseline to the end of the Titration (SP667 only) and Maintenance Phases

2.2.3 What are the characteristics of exposure/effectiveness relationships in patients with partial seizures?

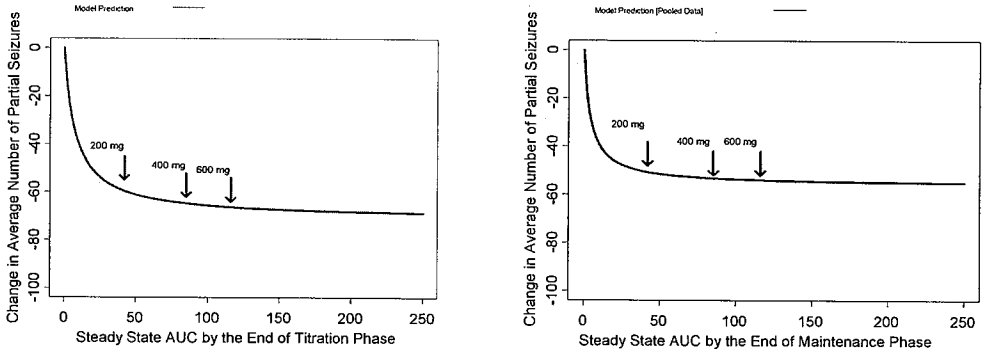
This has been reviewed by the Pharmacometrics reviewer. Please Refer to Dr Hao Zhu's review for details of the analysis.

The exposure-response relationship for lacosamide in treating patients with partial seizure is established in the responder patient population based on clinical observations in 3 clinical effectiveness studies (SP667, SP754, and SP755). Subjects with no evaluable slope for the baseline phase, or R^2 for the slope at baseline phase less than 0.95 were defined as nonresponders and were excluded from exposure-response dataset by the sponsor.

Our analyses are focused on observations at two critical time points, i.e. by the end of titration phase and by the end of maintenance phase. The exposure is defined as area under the curve (AUC) over a dosing interval of 12 hours at steady state. The response is defined as change from baseline of the average daily number of partial seizure.

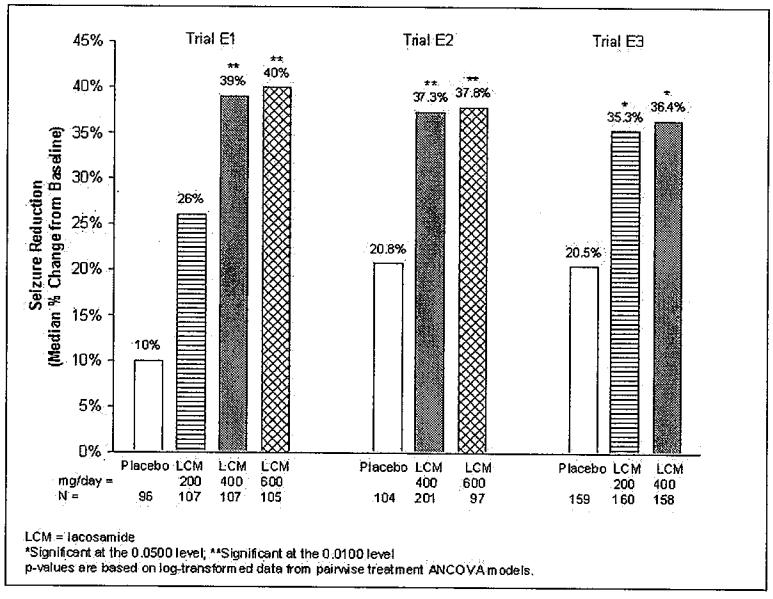
An Emax model is applied to describe the exposure-effectiveness relationship by using nonlinear least square regression ($P < 0.0001$). The model fitted curves are presented in the following Figure. The response curve started to flatten out beyond the median exposure of 400 mg dose based on the observed exposure-response relationship. Therefore, 600 mg dose does not appear to provide additional benefit compared to 400 mg dose.

Exposure-Response Relationship for Lacosamide in Treating Patients with Partial Seizure by the End of Titration Phase (A) and by the End of Maintenance Phase (B) (Responder's Analysis).



This is also supported by the sponsor's estimation of median percent reduction in seizure frequency as seen in the following Figure. This shows that LCM doses 400 and 600 mg has similar reductions in the seizure frequency.

Median Percent Reduction in Seizure Frequency per 28 days from Baseline to the Maintenance Phase by Dose



2.2.4 Are the proposed dosage regimens for partial seizures indications adequately supported by the clinical trial and consistent with the dose-response relationship?

b(4)

Yes. [redacted]

This has been reviewed by the Pharmacometrics reviewer/ Safety reviewer. Please see response to Question 2.2.3 as well and refer to Dr Hao Zhu's review.

2.2.5 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, all bioanalytical assay validations were adequately performed both for lacosamide and its metabolite, SPM12809 in plasma and urine. The method validations have been reviewed by Drs. Fadiran and Zhang. Study specific validations are reviewed with in the study. For further details refer to section 2.6 of this review.

2.2.6 What are the ADME characteristics of Lacosamide?

Tablets:

This has been reviewed by Drs Fadiran and Zhang. Please refer to their review for further details. Key characteristics are given below:

- Tmax for tablets occurred between 0.5-4 hours after dosing and was not influenced by multiple dosing.
- LCM has an absolute bioavailability of 100%.
- There is no effect of food on the rate and extent of LCM absorption.
- The apparent mean volume of distribution (V/f) was between 40-60 L across studies, indicating that LCM is distributed in total body water.
- Less than 15% of LCM is bound to plasma protein.
- LCM has a low metabolic turnover in vitro (<4% in 4 hours). Two metabolites, SPM 12809 (desmethyl) and SPM 6912 (desacetyl) were found in trace (<3%). However, a human radiolabeled ADME study (SP619) suggested that lacosamide was metabolized in vivo. Only 40% of unchanged LCM was recovered in urine and about 30% of the dose was recovered in urine as SPM 12809, the major metabolite. Another 20% of dose was polar fraction (structure unidentified). Small amounts of further metabolites (p-hydroxy-, O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and desacetyl-derivatives of LCM) representing 0.5% to 2% of the dose were also found in urine. In addition, an N-carbamoyl-O-ß-D-glucuronide of the desacetyl-metabolite was identified in SP619.
- Other in vivo data showed that lacosamide is close to 100% bioavailable indicating that first-pass is not significant. It is not clear where lacosamide is metabolized.

- The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. The sponsor incubated lacosamide with CYP2C19 ——— and identified two metabolites, SPM 12809 and SPM 6912. The Sponsor did not study other CYP isoforms in the recombinant systems. b(4)
- SPM 12809 being major detectable inactive metabolite, representing about 10% of the parent exposure in plasma. CYP2C19 is involved in the formation of this metabolite.
- The t1/2 of LCM tablets is about 13 hours (Geometric mean range is 11-16 hours, absolute values range is 7.4-20.76), the t1/2 of SPM12809 is between 15-23 hours.
- Approximately 95% of the administered radioactivity was recovered in urine and less than 0.5% in feces, indicating renal excretion is the major pathway of elimination.

Solution for Infusion:

The key ADME characteristics of solution for infusion were similar to oral lacosamide tablets and are summarized below:

After a single dose of 200 mg, the pharmacokinetic parameters (**absorption and elimination**) of the iv solution for injection at a 60 minute infusion rate was similar to the oral lacosamide as seen in the following Table. For comparisons of other different infusion rates (15 and 30 minutes), please refer to section 2.5.1 on page 44 of this review.

Pharmacokinetic parameters: mean (CV) of LCM after administration of 200mg LCM as single dose

Parameter	IV Lacosamide	Oral Lacosamide
AUC (0-tz) (μg.hr/mL)	95.84 (14.9)	96.87 (19.2)
AUC (0-∞) (μg.hr/mL)	98.58 (14.9)	100.0 (19.4)
Cmax (μg/mL)	5.72 (8.6)	6.209 (32.4)
t1/2 (h)	13.63 (9.1)	13.78(9.8)
F (%)	NA	101.4 (7.2)
Ae (mg)	46.38 (9.1)	45.33 (18.2)

After oral and IV administration of 100mg [^{14}C]-lacosamide in healthy subjects, approximately 95% of the administered radioactivity was recovered in urine and less than 0.5% in feces.

Cumulative Recovery of Radioactivity (Mean ± SD, N=5 at 168 hr post dose).

Route	Total Recovery in Urine (% of Dose)	Total Recovery in Feces (% of Dose)	Total Recovery (% of Dose)
IV	96.8 ± 2.6	0.3 ± 0.1*	97.1 ± 2.7
Oral	94.2 ± 3.1	0.4 ± 0.2*	94.6 ± 3.1

PK studies also showed that at steady state, approximately 30% to 40% of the administered dose is excreted into urine as unchanged LCM and approximately 20% to 30% as SPM 12809

The pharmacokinetics of the major inactive metabolite SPM12809 after a single dose is also similar between the iv and oral administration as seen in the following Table:

Pharmacokinetic parameters: mean (CV) of SPM12809 after administration of 200mg LCM as single dose

Parameter	IV Lacosamide	Oral Lacosamide
AUC (0-tz) (µg.hr/mL)	10.04 (34.9)	10.26 (51)
AUC (0-∞) (µg.hr/mL)	11.039 (35)	12.97 (29.2)
Cmax (µg/mL)	0.267 (37)	0.377 (68)
t1/2 (h)	17.75 (26.1)	17.30 (35.8)
CL	285 (35)	242.54 (29.2)
Ae (mg)	18.52 (41.5)	16.78 (37.6)

The **distribution** of lacosamide was also similar after iv and oral administration. The volume of distribution after single iv and oral administration is shown in the following Table:

Volume of distribution (V/f) of LCM following single intravenous and oral administrations in healthy male subjects – SP834, SP587, and SP588

Route of adminis-tration	50mg	100mg	150mg	300mg	400mg	500mg	600mg	800mg	Trial no.
	Arithmetic mean ± standard deviation of V_d[a] (L)								
iv	48.6 ±6.8 (N=6)	39.4 ±5.0 (N=6)	43.3 ±5.1 (N=6)	48.5 ±5.4 (N=5)	n.d.	n.d.	n.d.	n.d.	SP834
oral	n.d.	n.d.	n.d.	n.d.	54.89 ±14.08 (N=12)	n.d.	51.23 ±11.23 (N=12)	48.92 ±10.08 (N=9)	SP587
	n.d.	n.d.	n.d.	45.12 ±9.45 (N=14)	n.d.	57.11 ±22.66 (N=10)	n.d.	n.d.	SP588

a V_d for intravenous administration and V/f (apparent volume of distribution) for oral administration

After iv administration as well as after oral administration, the V_d of LCM was between approximately 40 and 60L, indicating that LCM is distributed in the total body water. A similar volume of distribution after iv and oral administration confirms the high bioavailability of LCM after oral administration.

The **metabolism of the iv** lacosamide and oral tablets were also similar. The metabolism of both iv and oral lacosamide was evaluated in poor and extensive metabolizers (Study SP643). The AUC of parent and metabolite were compared for both dosage forms, as seen in the following tables. These tables show that CYP2C19 is involved in the metabolism of lacosamide since the metabolite concentration is reduced in the poor metabolizers. Although LCM is not increased to similar extent, suggesting other pathways are also involved in the metabolism of LCM. The extent of metabolism is similar in the two routes of administration.

AUC comparisons in poor and extensive metabolizers after intravenous and oral dosing-SP643

AUC(0-tz) after intravenous dosing [h*µg/mL]

	PM (N=3)	EM (N=8)	Ratio (PM/EM)	Difference PM-EM
SPM 927	101.74	95.84	1.06	+ 6.15%
SPM12909	1.92	10.04	0.19	-80.88%

AUC(0-tz) after oral dosing [h*µg/mL]

	PM (N=3)	EM (N=8)	Ratio (PM/EM)	Difference PM-EM
SPM 927	106.6	96.9	1.10	+ 10.01%
SPM12909	2.44	10.30	0.23	-76.31%

A radiolabeled study (SP619 reviewed by Dr. Fadiran) also showed that the amounts of parent LCM and its metabolite formation were similar in plasma and urine following both oral and iv administrations as seen in the following Table, although metabolite SPM 12809 was not detected in this study, but was detected in other studies (SP757 and SP643):

Amounts of the parent compound LCM and its metabolites in plasma and urine following single oral and iv administration-SP619

Compound (code)	Plasma		Urine	
	oral (N=5)	iv (N=5)	oral (N=5)	iv (N=5)
	Median (range) in % of sample radioactivity			
LCM (SPM 927)	71.1 (61.2-100)	74.4 (71.2-81.2)	33.9 (30.0-45.6)	39.7 (31.2-46.0)
O-desmethyl-metabolite (SPM 12809)	2.4 (0-7.6)	n.d.	31.8 (21.3-42.5)	30.0 (25.3-35.2)
Polar fraction	0 (0-2.2)	n.d.	18.1 (15.2-25.0)	19.6 (17.7-24.7)
p-hydroxy-metabolite	n.d.	n.d.	0.8 (0-1.3)	0.8 (0-1.9)
O-desmethyl-p-hydroxy-metabolite	n.d.	n.d.	1.6 (0-2.3)	0 (0-1.6)
O-desmethyl-m-hydroxy-metabolite	n.d.	n.d.	2.0 (1.1-3.1)	2.1 (0-2.6)
Desacetyl-metabolite (SPM 6912)	n.d.	n.d.	0.8 (0-2.4)	2.6 (0-2.9)

The radiolabeled study was not able to detect the metabolite SPM12809, probably due to the assay methodology (liquid scintillation versus LC/MS/MS, because in the non-labeled study described (SP643) above similar amounts of this metabolite was formed via both routes of administration.

2.2.7 What are the basic pharmacokinetic parameters of lacosamide after single and multiple doses?

Tablets:

Single Dose Pharmacokinetics:

This has been reviewed by Drs Fadiran and Zhang. For details please refer to their review. The single dose pharmacokinetic parameters for lacosamide from two studies for doses 100-800 mg is shown in the following Tables:

Pharmacokinetic parameters of LCM following single administrations of 100, 200, 400, and 600mg LCM in healthy male subjects-Study SP835

Parameter (unit)	Statistic	100mg N=6	200mg N=6	400mg N=6	600mg N=5[a]
$AUC_{(0-tz)}$ (µg/mL*h)	Median (range)	41.98 (36.26-54.25)	85.87 (68.57-111.03)	180.46 (130.27-192.86)	255.87 (184.50-310.44)
$AUC_{(0-\infty)}$ (µg/mL*h)		45.43 (39.35-65.23)	94.31 (72.20-124.27)	195.48 (136.50-217.70)	297.70 (190.49-356.36)
C_{max} (µg/mL)		2.26 (1.93-2.56)	4.55 (4.35-5.73)	8.63 (7.46-9.37)	11.50 (11.44-14.80)
$t_{1/2}$ (h)		13.31 (12.52-18.10)	12.93 (8.62-14.40)	12.36 (9.72-15.10)	14.99 (9.45-16.80)
t_{max} (h)		2.0 (1-4)	3.0 (2-4)	3.0 (3-4)	3.0 (3-3)

- A comparison of $AUC_{(0-tz)}$ and C_{max} between the dose groups presented in the table above shows that the PK parameters increased proportionally with the dose.

Pharmacokinetic parameters of LCM following single oral administrations of 400, 600, and 800mg LCM in healthy male subjects – SP587

Parameter (unit)	Statistic	400mg	600mg	800mg
		N=12	N=12	N=9[a]
$AUC_{(0-tz)}$ (µg/mL*h)	Geometric mean (CV%)[b]	137.36 (19.4)	221.64 (21.8)	288.09 (25.9)
$AUC_{(0-\infty)}$ (µg/mL*h)		141.02 (19.0)	226.15 (22.0)	293.24 (26.5)
C_{max} (µg/mL)		8.53 (20.2)	14.16 (16.1)	18.43 (26.0)
$t_{1/2}$ (h)		13.04 (16.5)	13.10 (8.1)	12.20 (11.4)
t_{max} (h)	Median (range)	1.50 (1.0-4.0)	1.00 (1.0-4.0)	2.00 (1.0-2.0)
CL/f (L/h)	Geometric mean (CV%)[b]	2.84 (19.0)	2.65 (22.0)	2.73 (26.5)
A_e (mg)	Arithmetic mean ±SD	84.92 ±10.72	144.41 ±27.50	198.52 ±51.64
CL_{renal} (L/h)		0.66 ±0.16	0.70 ±0.20	0.76 ±0.31

Multiple Dose Pharmacokinetics:

The repeat dose pharmacokinetic parameters for lacosamide from three studies for 200 mg dose is shown in the following Table:

Pharmacokinetic parameters of LCM and SPM 12809 following repeated oral administrations of 200 mg LCM twice daily at steady state-SP640, SP660 and SP661

Trial (no. of subjects)	Parameter (unit)	Statistic	LCM	SPM 12809
SP640[a] (N=57)	$AUC_{(0-12)ss}$ (µg/mL*h)	Geometric mean (CV%)	100.32 (17.6)	14.08 (44.6)
	$C_{max,ss}$ (µg/mL)		10.92 (16.8)	1.28 (44.5)
SP660[b] (N=16)	$AUC_{(0-12)ss}$ (µg/mL*h)		76.69 (20.81)	11.17 (57.6)
	$C_{max,ss}$ (µg/mL)		9.22 (17.40)	0.99 (57.9)
SP661[c] (N=12)	$AUC_{(0-12)ss}$ (µg/mL*h)		94.95 (17.3)	8.35 (43.2)
	$C_{max,ss}$ (µg/mL)		11.70 (16.2)	0.81 (43.7)

CV=coefficient of variation; LCM=lacosamide

Tmax and terminal half-life of LCM after multiple doses were similar to those after single dose.

Pharmacokinetic parameters of LCM following single and multiple administrations of 300 and 500mg LCM in healthy male subjects (Study SP588).

Parameter (unit)	Statistic	Single dose		Multiple dose[a]	
		300mg	500mg	300mg bid	500mg bid
		N=14[b]	N=10[b]	N=12	N=4[c]
$AUC_{(0-tz)}$ (µg/mL*h)	Geometric mean (CV%)[d]	104.05 (13.0)	159.26 (39.8)	n.d.	n.d.
$AUC_{(0-12)}$ (µg/mL*h)		n.d.	n.d.	124.87* (14.2)	130.39[e] (14.89-196.26)
$AUC_{(0-\infty)}$ (µg/mL*h)		110.81 (14.2)	177.35 (44.0)	n.d.	n.d.
C_{max} (µg/mL)		7.34 (26.0)	9.88 (37.4)	14.36* (11.5)	15.25[e] (1.78-21.80)
$t_{1/2}$ (h)		11.30 (24.0)	13.35 (27.1)	12.01 (23.6)	8.73[e] (7.60-15.21)
t_{max} (h)	Median (range)	1.00 (0.5-4.0)	1.00 (0.5-2.0)	1.00 (1.0-2.0)	1.50[e] (0.0-2.0)
CL/f (L/h)	Geometric mean (CV%)[d]	2.71 (14.2)	2.82 (44.1)	2.40 (14.2)	3.84[e] (2.55-33.58)
A_e (mg)	Arithmetic mean ±SD	167.30 ±53.39[e]	263.74 ±132.70	237.66 ±88.46[g]	171.95[e] (31.81-383.30)
CL_{renal} (L/h)		1.48 ±0.44[f]	1.38 ±0.42	1.82 ±0.56[g]	1.71[e] (1.18-2.14)

2.2.8 Do the pharmacokinetic parameters change with time following chronic dosing?

This has been reviewed by Drs Fadiran and Zhang. For details please refer to their review.

Tablets:

- The comparability of $AUC_{(0-\infty)}$ after single-dose administration and $AUC_{\tau,ss}$ after multiple-dose administration shows that the pharmacokinetics of LCM do not change during multiple-dose administration (see previous Tables for a 200 mg dose)

- Following twice-daily dosing, the plasma concentration increases with an accumulation factor of approximately 2.3 for C_{max} and $C_{max,ss}$, and is consistent with what is estimated from its apparent half-life of 13 hours assuming one-compartment model. Also see Figure in section 2.2.11.

- The t1/2 of LCM and SP12809 also do not change after single or multiple doses of LCM

- Steady state concentrations of LCM are reached after 3 days of twice daily dosing. The trough concentration on Day 4 and 9 are shown in the following Table:

Trough plasma concentrations of LCM at steady state in healthy subjects – SP603 and SP661

Trial	LCM dose	Time point	N	C_{trough} (µg/mL)	$C_{max,ss}$ (µg/mL)	Ratio "$C_{trough}/C_{max,ss}$" (%)
				Arithmetic means±SD		
SP603[a]	200mg bid	Day 9	10	5.70±0.83	9.78±1.30	58.28%
SP661[b]		Day 4	12	5.58±1.07	11.85±2.04	47.09%

bid=bis in die (twice daily); LCM=lacosamide; SD=standard deviation

Solution for Infusion:

The maximum duration of infusion has been up to 5 days, with PK samples taken only after two days of infusion.

2.2.9 What is the variability in the PK data?

The inter subject variability in the pharmacokinetic parameters was similar for all the dosage forms (tablets, — and solution for infusion) based on cross-study comparisons. The CV% ranged between 16-36% for all parameters. b(4)

2.2.10 How do the pharmacokinetics of the drug in healthy volunteers compare to that in epilepsy patients?

Tablets:

The LCM plasma concentrations showed dose proportionality in the patient population as well, as seen in the following Table.

Mean plasma concentrations of LCM (μg/mL) - SP667, SP755, SP754,

Trial	LCM dose	Visit	N	Mean±SD
Adults with partial-onset seizures				
SP667	200mg/day	Visit 12	71	5.26±2.21
	400mg/day	(End of MP)	67	9.64±4.16
	600mg/day		41	13.63±6.21
SP755	200mg/day	Visit 8	135	3.77±1.90
	400mg/day	(End of MP)	98	7.35±3.88
SP754	400mg/day	Visit 9	123	7.19±2.92
	600mg/day	(End of MP)	35	9.50±4.29

Predose plasma concentrations at steady state (C_{trough}) for subjects with partial-onset seizures are compared with data for healthy subjects in the following table.

Trough plasma concentrations of LCM at steady state in subjects with epilepsy and healthy subjects

Trial no.	Subject population	Dose	Time point	N	C_{trough} (μg/mL)
					Arithmetic mean±SD
SP603	Healthy subjects	200mg bid	Day 9	9[a]	5.7±0.83
SP661			Day 4	12[b]	5.6±1.1
SP586	Subjects with epilepsy		Day 15[c]	13	5.8±2.4

a Data for Sequence Group 2 (starting with LCM prior to coadministration of carbamazepine) are shown for SP603.
b Data for the group of White subjects are shown for SP661.
c Data from the predose sample taken on Day 15 after 2-week treatment with 200mg LCM twice daily are shown for SP586.

As shown in the table above, predose plasma concentrations of LCM in the target populations were comparable to those observed in healthy subjects at steady state.

Population PK analyses (reviewed by Dr. Hao) based on data collected in the epilepsy population showed that the mean population PK parameter estimates for k_e ($t_{1/2}$) and V/f in the target populations were about 40-50% different with PK parameters determined in Phase 1 trials in healthy subjects by population PK analyses. The V and t1/2 were 40-50% higher in the epilepsy patient population compared to the healthy subjects, as seen in the Table below. The LCM population PK parameters showed low interindividual variability in the target populations as well as in healthy subjects, but was a little higher in the epilepsy patient population compared to the healthy subjects.

PK parameters in patients with epilepsy and healthy subjects

Parameters (Unit)	Population	Trial	Final Estimates in a typical Subjects	Interindividual Variability (%)
V/F (L)	Healthy Subjects	SP640	43.4	6.25
		SP620	39.6	3.56
	Patients with Partial Seizure	SP755	60	6.57
		SP754	68.4	9.52
	Patients with Diabetic Neuropathy	SP665	39.6	14
		SP742	48.3	10.1
		SP743	44.2	15.8
Ke (1/h)	Healthy Subjects	SP640	0.045	13.1
		SP620	0.0451	4.12
	Patients with Partial Seizure	SP755	0.0333	19.1
		SP754	0.029	21.4
	Patients with Diabetic Neuropathy	SP665	0.0428	20.2
		SP742	0.035	22.2
		SP743	0.0364	27.6
t1/2 (h)	Healthy Subjects	SP640	15.4	13.1
		SP620	15.4	4.12
	Patients with Partial Seizure	SP755	20.8	19.1
		SP754	23.9	21.4
	Patients with Diabetic Neuropathy	SP665	16.2	20.2
		SP742	19.8	22.2
		SP743	19	27.6

It is interesting to note that the patients with diabetic neuropathy has V and t1/2 comparable to the healthy subjects. The reasons for differences seen in the epilepsy patient population and healthy volunteers is not clear.

Solution for Infusion:

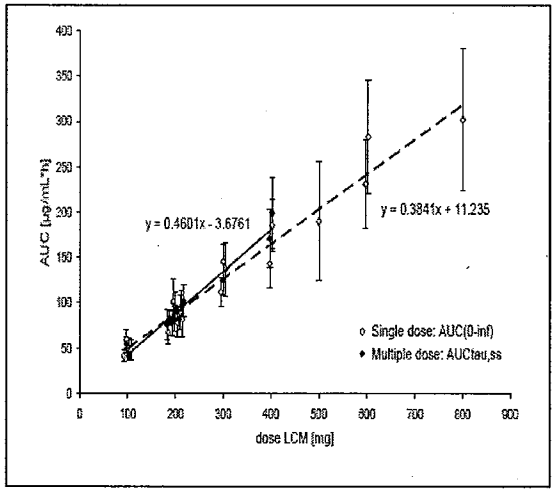
A cross study comparison of the pharmacokinetics after iv administration (30 minute infusion) in healthy subjects and in epilepsy patients showed that the Cmax's were similar in these population at equivalent doses of 200 mg/day. The Cmax in subjects was 6 (2.8-8.5) µg/mL and the Cmax in epilepsy patients was 5.23(3.8-7.09) µg/mL. Due to limited sampling in patients after iv dosing, comparison of other pharmacokinetic parameters could not be made.

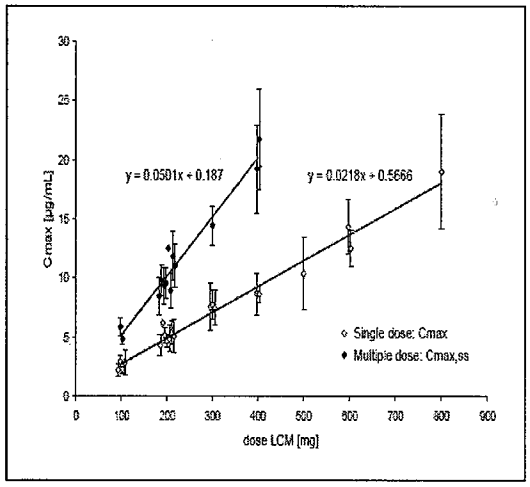
2.2.11 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Tablet:

This has been reviewed by Drs Fadiran and Zhang. Please refer to their review for details. In summary lacosamide was dose proportional after both single and multiple dose administration of 100-800 mg LCM tablets, as seen in the following figures:

Dose-proportional increase of $AUC_{(0-\infty)}$ and C_{max} after single-dose administration and of $AUC_{\tau,ss}$ and $C_{max,ss}$ after multiple-dose administration of LCM – healthy subjects

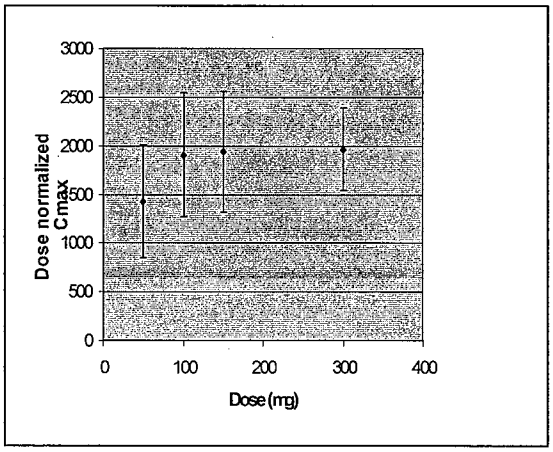


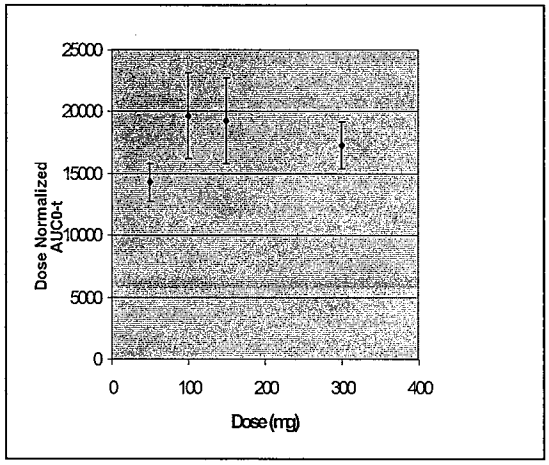


Solution for Infusion:

The sponsor has conducted a study (Study SP834) evaluating the pharmacokinetics of single ascending IV doses, but not with the to-be-marketed formulation. No formal assessment of dose linearity has been made from this study, but the Cmax and AUC0-t appear to increase approximately in a dose proportional manner as seen the figures below for dose normalized parameters.

Dose-normalized $AUC_{(0-t)}$ and C_{max} of IV administration-SP834





2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 Effect of Renal Impairment: (reviewed by Dr. Zhang)

Mean AUC increased 27%, 23%, and 59% in subjects with mild, moderate, and severe renal impairment compared with healthy subjects, respectively. AUC values were more variable for patients with severe renal impairment, AUC in some patients were 2-fold higher than AUC in healthy subjects. Renal clearance of lacosamide decreased with increasing degree of renal impairment.

For C_{max}, only a slight difference was observed. The terminal half-life of lacosamide in plasma ($t_{1/2}$) was prolonged in subjects with severe renal impairment (approximately 18 hours) in comparison with healthy subjects (approximately 13 hours)

Pharmacokinetic parameters of lacosamide in healthy subjects compared with subjects with mild to severe renal impairment.

Parameter (unit)	Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
	Geometric mean (CV %)			
$AUC_{(0\text{-}tz)}$ (µg/mL*h)	47.01 (20.8)	59.62 (17.5)	57.57 (19.0)	74.76 (26.9)
$AUC_{(0\text{-}tz)norm}$ (µg/mL*h*kg)	3525 (15.4)	4916 (24.0)	4085 (20.0)	5196 (27.4)
C_{max} (µg/mL)	2.69 (35.0)	2.95 (20.7)	3.06 (10.0)	3.02 (23.3)
$C_{max,norm}$ (µg/mL*kg)	202 (22.2)	243 (16.7)	217 (10.3)	210 (17.4)
t_{max} (h) [a]	1.00 (0.5-2.0)	0.50 (0.5-1.0)	0.50 (0.5-1.0)	1.00 (0.5-1.5)
CL/f (L/h)	2.13 (20.8)	1.68 (17.5)	1.74 (19.0)	1.34 (26.9)
CL_R (L/h)	0.5897 (37.9)	0.3544 (51.3)	0.2766 (24.4) [c]	0.1428 (31.8)
$A_{e(0\text{-}48)}$ (mg) [b]	28.86±7.72	22.89±8.29	15.93±3.10 [c]	11.35±2.70
$t_{1/2}$ (h)	13.22 (17.6)	18.17 (18.7)	15.39 (18.9)	18.30 (27.8)
$t_{1/2,ur}$ (h)	13.94 (3.1)	13.92 (1.5)	14.09 (3.6) [c]	14.33 (5.2)

CV=coefficient of variation; PKS=Pharmacokinetic Set
Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment

ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for lacosamide.

Parameter	Ratio	Point estimate	90% confidence interval
$AUC_{(0-tz)}$	"Group 2 / Group 1"	1.2682	(1.0601, 1.5172)
	"Group 3 / Group 1"	1.2247	(1.0237, 1.4651)
	"Group 4 / Group 1"	1.5903	(1.3293, 1.9025)
$AUC_{(0-tz)norm}$	"Group 2 / Group 1"	1.3946	(1.1581, 1.6794)
	"Group 3 / Group 1"	1.1591	(0.9625, 1.3958)
	"Group 4 / Group 1"	1.4741	(1.2241, 1.7751)
C_{max}	"Group 2 / Group 1"	1.0955	(0.8972, 1.3375)
	"Group 3 / Group 1"	1.1356	(0.9301, 1.3866)
	"Group 4 / Group 1"	1.1223	(0.9192, 1.3703)
$C_{max,norm}$	"Group 2 / Group 1"	1.2047	(1.0422, 1.3924)
	"Group 3 / Group 1"	1.0748	(0.9299, 1.2423)
	"Group 4 / Group 1"	1.0403	(0.9000, 1.2024)

ANOVA=analysis of variance
Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment

The plasma concentrations of the metabolite, SPM 12809, also increased with increasing degree of renal impairment. The increases were more profound than lacosamide. AUC increased 4-fold in patients with severe renal impairment compared to normal renal function subjects.

Pharmacokinetic parameters of SPM 12809 in healthy subjects compared with subjects with mild to severe renal impairment.

Parameter (unit)	Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
	Geometric mean (CV %)			
$AUC_{(0-tz)}$ (µg/mL*h)	7.63 (58.5)	11.59 (62.1)	27.46 (20.8)	35.36 (51.6)
$AUC_{(0-tz)norm}$ (µg/mL*h*kg)	572 (52.3)	956 (65.0)	1948 (29.8)	2458 (54.5)
C_{max} (µg/mL)	0.19 (63.7)	0.20 (42.6)	0.45 (22.1)	0.49 (55.9)
$C_{max,norm}$ (µg/mL*kg)	14.29 (54.9)	16.20 (42.7)	31.70 (28.1)	33.91 (57.7)
t_{max} (h) [a]	12.0 (8-24)	24.0 (12-48)	24.0 (24-36)	36.0 (24-60)
CL/f (L/h) [b]	13.11 (58.5)	8.63 (62.1)	3.64 (20.8)	2.83 (51.6)
CL_R (L/h) [b]	2.27 (28.7)	0.79 (99.9)	0.51 (53.7) [c]	0.12 (52.5) [c]
$A_{e(0-48)}$ (mg) [d]	19.38±6.67	11.78±4.15	17.23±5.28 [c]	6.92±3.81
$t_{1/2}$ (h)	15.69 (20.8)	28.76 (37.4)	29.61 (36.0)	56.06 (40.2) [c]

ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for SPM 12809.

Parameter	Ratio	Point estimate	90% confidence interval
$AUC_{(0-tz)}$	"Group 2 / Group 1"	1.5201	(1.0156, 2.2750)
	"Group 3 / Group 1"	3.6002	(2.4055, 5.3883)
	"Group 4 / Group 1"	4.6372	(3.0983, 6.9403)
C_{max}	"Group 2 / Group 1"	1.0306	(0.7001, 1.5171)
	"Group 3 / Group 1"	2.3429	(1.5916, 3.4489)
	"Group 4 / Group 1"	2.5591	(1.7385, 3.7672)

ANOVA=analysis of variance;
Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment

Under a 4-hour dialysis starting 2.5 hours after dosing, $AUC_{(0-tz)}$ of LCM and SPM 12809 was approximately 50% lower in subjects with endstage renal disease (ESRD) receiving hemodialysis after a single oral dose of 100mg LCM compared with dosing on a dialysis-free day. C_{max} was less affected by dialysis than AUC, probably because the maximum plasma concentration was reached before the start of dialysis in most subjects.

Pharmacokinetic parameters of lacosamide after Treatments A and B in subjects with end-stage renal disease, requiring dialysis.

Parameter (unit)	Treatment A (N=8)	Treatment B (N=8)
	Geometric mean (CV %)	
$AUC_{(0-tz)}$ (µg/mL*h)	43.19 (20.2)	23.19 (15.1)
$AUC_{(0-tz)norm}$ (µg/mL*h*kg)	3056 (17.1)	1641 (17.9)
C_{max} (µg/mL)	3.18 (22.4)	2.79 (22.1)
$C_{max,norm}$ (µg/mL*kg)	225 (13.6)	197 (17.3)
t_{max} (h) [a]	0.5 (0.50-4.0)	0.75 (0.50-2.0)
$t_{1/2}$ (h)	19.55 (19.4)	19.24 (26.8)
Extraction rate (%) [b]	NA	57.44±2.56
CL_{dial} t=4h (mL/min)	NA	140.83 (11.7)
CL_{dial} t=6.5h (mL/min)	NA	140.36 (8.9)
Amount excreted by dialysis (mg) [b]	NA	50.9±6.3

CV=coefficient of variation; NA=not applicable; Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis);
Treatment B=single dose of 100mg lacosamide 2.5 hours before start of dialysis
a Median (range)
b Arithmetic mean±standard deviation

Dosage adjustment:
Dose adjustment for patients with mild and moderate renal impairment may not be needed. However for patients with severe renal impairment, due to a mean 60% increase in AUC and highly variable data, the highest doses in severe renal impairment patients should be reduced to → of the highest doses recommended in patients who have normal renal function. b(4)

2.3.1. 2 Effect of Hepatic Impairment: (reviewed by Dr. Zhang)

Plasma concentrations of lacosamide were approximately 50-60% higher in the subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Plasma concentrations of the main metabolite of lacosamide, SPM 12809, were approximately 40-50% lower in subjects with hepatic impairment compared to healthy subjects. PK of lacosamide has not been studied in mild or severe hepatic impairment patients. Caution should be exercised as metabolism of lacosamide is anticipated to be altered in these subjects.

Pharmacokinetic parameters (geometric means and % coefficient of variation) after multiple oral administration of 100mg lacosamide twice daily at steady state (Day 5).

Parameter (unit)	Lacosamide		SPM 12809	
	Group 1 (N=8)	Group 2 (N=8)	Group 1 (N=8)	Group 2 (N=8)
$AUC_{(0-12)ss}$ (µg/mL*h)	53.25 (17.3%)	85.89 (21.7%)	4.64 (54.8%)	2.64 (97.4%)
$AUC_{(0-12)ss,norm}$ (µg/mL*h*kg)	3747.75 (24.0%)	5508.56 (18.6%)	326.38 (51.2%)	169.61 (86.2%)
$C_{max,ss}$ (µg/mL)	5.83 (13.3%)	8.75 (18.7%)	0.41 (54.4%)	0.24 (97.8%)
$C_{max,ss,norm}$ (µg/mL*kg)	410.01 (19.8%)	561.23 (15.2%)	29.16 (50.5%)	15.41 (86.8%)
$t_{max,ss}$ [a] (h)	1.5 (0.5-2.0)	1.5 (0.5-2.0)	6.0 (4.0-8.0)	5.0 (3.0-12.0)
$t_{1/2}$ (h)	14.8 (19.7%)	24.1 (23.5%)	18.5 (17.4%)	29.2 (39.1%)
$A_{e(0-12)ss}$ [b] (mg)	43.96 (30.1%)	35.51 (62.4%)	16.57 (37.0%)	4.85 (51.1%)

Group 1=healthy subjects; Group 2=subjects with moderate hepatic impairment (Child-Pugh stage B)
a Median (range)
b Arithmetic mean (% coefficient of variation)

Summary of analysis of variance of log-transformed pharmacokinetic parameters for lacosamide and SPM 12809 at steady state (Day 5) for the comparison "Moderate Impairment"/"Normal".

Parameter	Lacosamide		SPM 12809	
	Ratio	90% CI	Ratio	90% CI
$AUC_{(0-12)ss}$	161%	136-191%	57%	31-104%
$AUC_{(0-12)ss,norm}$	147%	122-177%	52%	30-90%
$C_{max,ss}$	150%	130-173%	58%	32-106%
$C_{max,ss,norm}$	137%	117-160%	53%	30-92%
$A_{e(0-12)ss}$	71%	47-109%	28%	19-42%

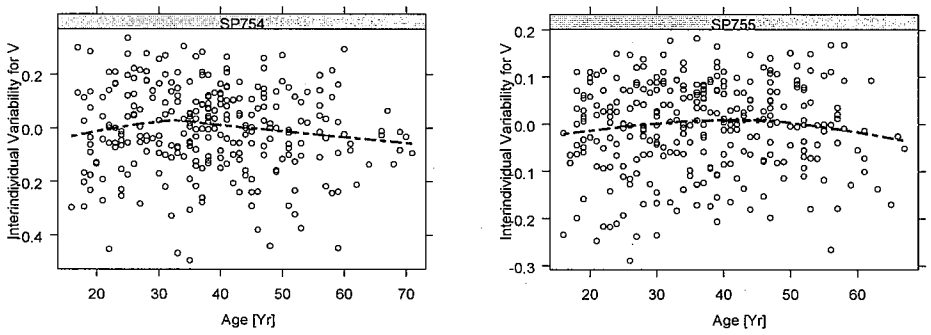
b(4)

Dosage adjustment:
The highest doses in moderate hepatic impairment patients should be reduced to — of the highest doses recommended in patients who have normal hepatic function.

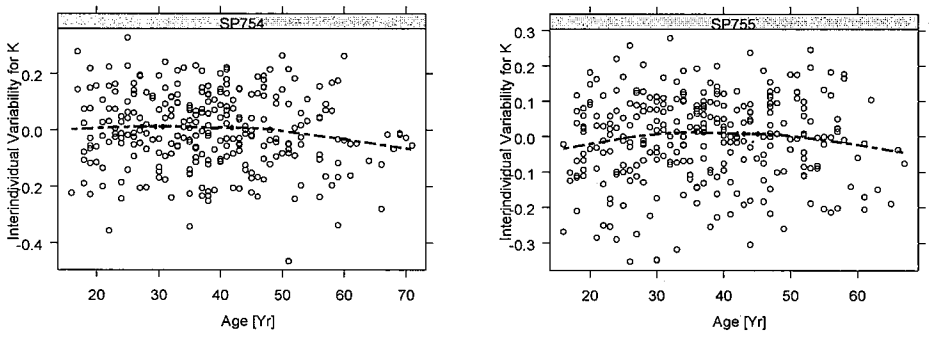
2.3.1. 3 Effect of age: (reviewed by Dr. Zhang and Zhu)

Elderly:
The exposure is ~30% higher in the elderly males and females compared to young males. When taking weight into account, there is a 20-25% difference between the elderly and young subjects.
Age does not influence exposure in patients with partial seizure based on population PK analyses results. The difference between individual and population mean parameter (called as inter-individual variability) for volume of distribution and Ke versus age is given in the Figure below. No specific trend can be identified.

Interindividual Variabilities for Vc and Ke versus Age



(A). IIV on V ~ Age for Study SP754 and SP755



(B) IIV on Ke ~ Age for Study SP754 and SP755

Dosage adjustment:
About 30% higher exposure in elderly may not warrant a dose adjustment based on age. However, caution should be exercised because elderly patients usually may also have impaired renal and hepatic function.

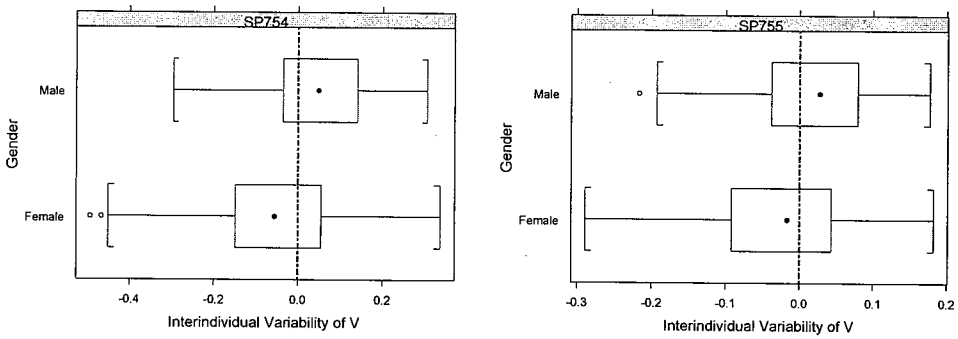
Pediatrics:

The pharmacokinetic profile of lacosamide in pediatric patients has not been established. Indication is sought in patients 16 years and older. Patients 16 and17 year olds have exposures similar to adults.
Dosing Adjustment:
No dosage adjustment necessary.

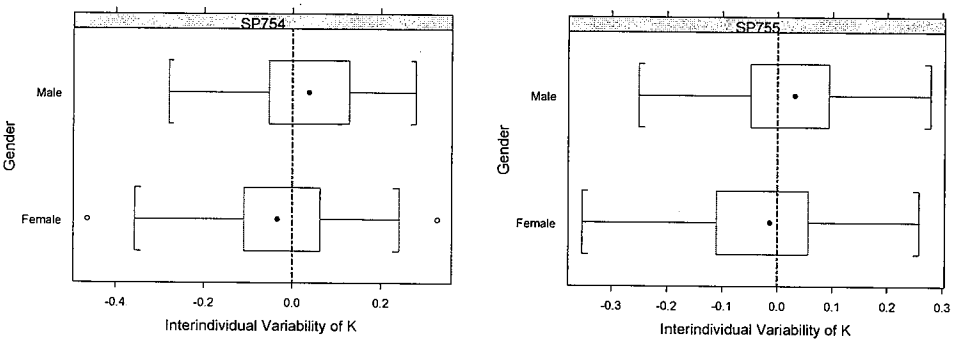
2.3.1.4 Effect of Gender: (reviewed by Dr. Zhang and Zhu)

Elderly female subjects showed ~15% higher AUC than elderly male subjects. Thee were no differences on taking body weight into consideration.
Sex does not influence exposure in patients with partial seizure based on population PK analyses results (see Figure below)

Interindividual Variabilities for Vc and Ke versus Gender



(A) IIV of Vc ~ Gender for Study SP754 and SP755



(B) IIV of Ke ~ Gender for Study SP754 and SP755

Dosage adjustment:
No dosage adjustment is necessary.

2.3.1.5 Effect of Race: (reviewed by Dr. Zhang)

A slightly higher exposure (measured as $AUC_{\tau,ss}$) of LCM was observed in Asian and Black compared with White subjects (increase of approximately 10%). The body weight was slightly higher in the group of White subjects, and after normalization to body weight ($AUC_{\tau,ss,norm}$) the exposure for the 3 ethnic groups was similar.

With respect to SPM 12809, mean $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max,ss}$, $C_{max,ss,norm}$ as well as $A_{e(0-12)}$ of SPM 12809 were approximately 30% to 50% lower in Asian and Black subjects compared with White subjects. This different is not considered clinically relevant because the exposure of SPM 12809 is lower in Blacks and Asians compared with White subjects and the metabolite of LCM has no known pharmacological activity.

Pharmacokinetic parameters of LCM and SPM 12809 after administration of 200mg LCM at steady state in Asian, Black, and White subjects – SP661

Parameter (unit)	Statistic	LCM			SPM 12809		
		Asian (N=12)	Black (N=12)	White (N=12)	Asian (N=12)	Black (N=12)	White (N=12)
$AUC_{\tau,ss}$ (µg/mL*h)	Geometric mean (CV%)	105.87 (15.6)	104.79 (19.2)	94.95 (17.3)	5.30 (49.1)	5.69 (62.9)	8.35 (43.2)
$AUC_{\tau,ss,norm}$ (µg/mL*h*kg)		7358 (15.6)	7327 (18.3)	7322 (20.5)	368.6 (51.8)	397.5 (58.5)	643.8 (39.4)
$C_{max,ss}$ (µg/mL)		12.03 (16.8)	11.82 (22.6)	11.70 (16.2)	0.480 (47.7)	0.516 (62.5)	0.814 (43.7)
$C_{max,ss,norm}$ (µg/mL*kg)		836.27 (16.8)	826.41 (20.6)	902.36 (18.1)	33.35 (50.0)	36.10 (58.3)	62.73 (39.7)
$t_{1/2}$ (h)		15.82 (10.0)	15.99 (8.8)	15.97 (15.9)	20.26 (16.3)	20.44 (14.5)	20.21 (19.5)
t_{max} (h)	Median (range)	0.8 (0.5-4)	0.5 (0.5-4)	0.8 (0.5-1.5)	2.0 (0.5-4)	2.5 (1.5-6)	1.8 (0.5-6)
$A_{e(0-12)}$ (mg)	Arithmetic mean ± SD	82.45[a] ±11.58	91.69[b] ±30.20	81.59 ±18.69	17.45[a] ±6.96	24.07[b] ±11.68	32.76 ±13.61

CV=coefficient of variation; LCM=lacosamide; SD=standard deviation
a N=8; b N=11

The point estimates of race comparison is given in the following Table:

Point estimates and 90% confidence intervals for AUC and C_{max} of lacosamide .

Parameter	Lacosamide	
	Ratio "Asian/White" (N=12)	Ratio "Black/White" (N=12)
$AUC_{t,ss}$	1.1150 (0.9896, 1.2562)	1.1037 (0.9795, 1.2435)
$AUC_{t,ss,norm}$	1.0050 (0.8869, 1.1388)	1.0008 (0.8832, 1.1340)
$C_{max,ss}$	1.0282 (0.9043, 1.1690)	1.0100 (0.8883, 1.1483)
$C_{max,ss,norm}$	0.9268 (0.8161, 1.0524)	0.9158 (0.8065, 1.0400)

Dosage adjustment:
No dosage adjustment is necessary.

2.3.1.6 Effect of CYP2C19 polymorphism

In vitro data suggested that CYP2C19 is involved in metabolism of lacosamide to form SPM 12809. Study SP643 compared the pharmacokinetics and bioavailability of LCM when given as iv solution or as oral tablet to 4 healthy Caucasian poor metabolizers (CYP2C19-genotyped) compared with 8 healthy Caucasian extensive metabolizers. PMs were homozygous for nonfunctional alleles and EMs were either heterozygous or homozygous for wild-type alleles. Data suggested that plasma concentrations of lacosamide were comparable (not more than 10% difference) between PMs and EMs, and there were noticeable differences (75-80% difference) between PMs and EMs with respect to AUCs of the metabolite SPM 12809.

AUC(0-tz) after oral dosing [h*µg/mL] and ratio PM/EM.

	PM (N=3)	EM (N=8)	Ratio (PM/EM)	Difference PM-EM
SPM 927	106.6	96.9	1.10	+ 10.01%
SPM12909	2.44	10.30	0.23	-76.31%

Based on these PK results, no dose adjustment is necessary in poor metabolizers of CYP2C19 or subjects who receive a CYP2C19-inhibiting drug in parallel to LCM.

2.4 EXTRINSIC FACTORS

2.4.1 Is lacosamide a substrate, inhibitor or inducer of CYP enzymes?

This was reviewed by Dr. Fadiran. Please refer to his review for further details.

Substrate: Lacosamide is a substrate to CYP2C19. Whether lacosamide is a substrate for CYP1A2, 2B6, 2C8, 2C9, 2D6, or 3A4 is unknown.

Inhibitor: Lacosamide did not inhibit 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, 3A5 at concentrations observed in the clinical trials. [In clinical trials with LCM doses of 200 to 600mg/day, plasma concentrations of LCM ranged from approximately 5 to 20μg/mL (corresponding to 20 to 80μM)].
In vitro studies showed a low inhibition potential for CYP2C19(About 59.9% inhibition of CYP2C19 at 100 μM, I/IC50 value for CYP2C19 was > 0.1 and sponsor conducted an in vivo study with omeprazole, a CYP2C19 substrate.

Inducer: Lacosamide induction potential on 1A2, 2B6, 2C9, 2C19, 3A4 was evaluated. LCM did not show induction for these CYPs at therapeutic relavent concetrations.

2.4.2 Is lacosamide a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

This was reviewed by Dr. Fadiran. Please refer to his review for further details.

Lacosamide was not a substrate for P-glycoprotein and did not modulate the transport of digoxin at concentrations up to 3mmol/L (750μg/mL).

The renal clearance of lacosamide (~ 2 L/hr) was less than GFR indicating that it was reabsorbed in the kidney. It is unknown which transporter may be responsible for the reabsorption of lacosamide.

2.4.3 Is there an in vitro basis to suspect drug-drug interaction?

The drug interaction potential for lacosamide is based on the following facts and :

- LCM is metabolized by CYP2C19.
- LCM is not significant inhibitor (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, 3A5), it inhibits CYP2C19 to some extent. An omeprazole (Substrate and inhibitor of CYP2C19) drug-drug interaction study was conducted to rule out inhibition potential of LCM on omeprazole and omeprazole on LCM.

- LCM not an inducer of any CYPS.
- Since <15% of LCM is bound to plasma proteins, a clinically relevant interaction with other drugs through competition to protein binding sites is unlikely.

2.4.4 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.4.1 Influence of lacosamide on other drugs:

This has been reviewed by Drs Fadiran and Zhang. Please refer to their reviews for additional details.

Influence of lacosamide on the pharmacokinetics of concomitant drugs is summarized in the following Table:

Concomitant Medication		Concomitant medication dose	Lacosamide doses evaluated	Cmax Ratio (90% CI) w/wo lacosamide	AUC Ratio (90%CI) w/wo lacosamide	Dosage Adjustment
Omeprazole		40 mg single dose	300 mg twice daily	1.1049 (0.9793, 1.2466)	1.0976 (0.9963, 1.2092)	None
Digoxin		0.25 mg QD	200 mg twice daily	1.0487 (0.9592, 1.1465)	1.0241 (0.9792, 1.0709)	None
Metformin		500 mg three times a day (0, 6, and 12 hr)	200 mg twice daily	Group 1 0.8782 (0.768, 1.004) Group 2 1.1725 (1.026, 1.340)	Group 1 0.8675 (0.773, 0.973) Group 2 1.1939 (1.064, 1.339)	None?
Oral Contra-ceptive (Micro-gynon)	ethniyl estradiol	0.03 mg 3 cycles	200 mg twice daily (the 3rd cycle)	1.205 (1.106, 1.312)	1.113 (1.052, 1.177)	None
	levonor-gestrel	0.15 mg 3 cycles	200 mg twice daily (the 3rd cycle)	1.120 (1.053, 1.192)	1.092 (1.046, 1.140)	None

Influence of other drugs on the pharmacokinetics of lacosamide/SPM12809 is summarized in the following Table:

Concomitant Medication	Concomitant medication dose	Lacosamide doses evaluated	LCM Cmax Ratio (90% CI) w/wo lacosamide	LCM AUC Ratio (90%CI) w/wo lacosamide	Dosage Adjustment
Omeprazole	40 mg QD	300 mg single dose	0.9958 (0.9474, 1.0467)	1.1330 (1.1015, 1.1654)	None
Metformin	500 mg three times a day (0, 6, and 12 hr)	200 mg twice daily	Group 1 1.1427 (1.044, 1.250) Group 2 1.0228 (0.935, 1.119)	Group 1 1.0964 (1.062, 1.132) Group 2 1.0280 (0.996, 1.061)	None

2.4.2.2 Influence of lacosamide on concomitant AEDs exposure:

In definitive drug interaction studies, the effect of LCM on carbamazepine and valproate was evaluated. No dosage adjustment was necessary for either drugs.

Concomitant Medication	Concomitant medication dose	Lacosamide doses evaluated	Cmax Ratio (90% CI) w/wo lacosamide % change	AUC Ratio (90%CI) w/wo lacosamide	Dosage Adjustment
Valproate	titrated from 300 to 600 mg	titrated from 100 to 400 mg	1.01 (0.97-1.07)	1.04 (0.99-1.09)	none
Carbamazepine	titrated from 200 to 400 mg	titrated from 200 to 400 mg	0.91 (0.87-0.98)	0.88 (0.84-0.92)	none
Carbamazepine-epoxide			0.95 (0.87-1.05)	0.97 (0.89-1.04)	

2.4.5.2 Influence of AEDs on lacosamide exposure:

The effect of concomitant AEDs on lacosamide exposure was evaluated for valproate and carbamazepine in definitive drug-drug interaction studies. No dosage adjustment for lacosamide was necessary.

Concomitant Medication	Concomitant medication	Lacosamide doses	Cmax Ratio (90% CI)	AUC Ratio (90%CI)	Dosage Adjustment

	dose	evaluated	w/wo AED % change	w/wo AED	
Valproate	titrated from 300 to 600 mg	400 mg	1.01 (0.96-1.07)	1.00 (0.98-1.03)	none
Carbamazepine	titrated from 200 to 400 mg	400 mg	1.075 (0.98-1.170)	1.011 (0.96-1.065)	none

The other concomitant antiepileptics were evaluated in a population analysis of the Phase 3 studies in patients with partial seizures. According to the sponsor based on the population analysis, LCM exposure is reduced by 15-20% when lacosamide is coadministered with carbamazepine, phenobarbital, or phenotyoin.

According to Dr. Zhu, drug-drug interaction covariate effects from population PK analysis are difficult to interpret. There is inadequate evidence to suggest that coadministration of carbamazepine alone affect lacosamide exposure based on the following two facts. 1.) In population PK analysis using data from patients with partial onset of seizure, the sponsor did not demonstrate statistical significance when using coadministration of carbamazepine alone as a covariate. 2.) A drug-drug interaction study with intensive PK sampling in healthy subjects did not show that concurrent administration of carbamazepine lead to lacosamide pharmacokinetic change.
Furthermore, there are several confounding factors in the defining the covariates. For example, about 80% (55 out of 69) patients in SP754 study who took carbamazepine concurrently took 1 or 2 other medications. It is unclear whether the significant covariate effect is driven by carbamazepine or some other drugs. This reduction is not likely to be clinical meaningful.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the formulations — —solution for injection) proposed for marketing and can they be used interchangeably?

b(4)

The sponsor is proposing to market — dosage forms of lacosamide, tablets, — and solution for injection. The — solution for injection are proposed for the epilepsy indication only, where as the tablets will be used for epilepsy as well as neuropathic pain.

b(4)

b(4)

b(4)

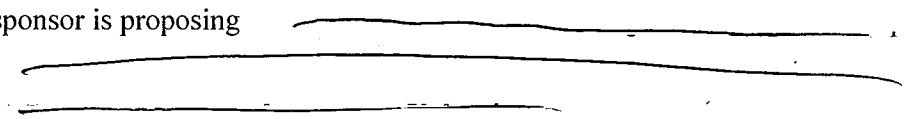
Tablet vs IV Solution for Injection:

In clinical practice the need may arise for a short-term replacement of oral therapy with lacosamide by therapy via an intravenous (iv) route, e.g., as pre- and postsurgery treatment. Hence, bioequivalence evaluation between the two routes of administration was conducted by the sponsor.

The following observations were made from the bioequivalence studies using infusion times of 15, 30 and 60 minutes:

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

The sponsor is proposing



b(4)

The sponsor conducted two bioequivalence studies (Studies SP645 and SP658) using different IV infusion rates versus the tablet formulation (2x100 mg).

The Pharmacokinetic parameters (arithmetic means) in these studies are shown in the Table below.

Pharmacokinetic parameters of LCM following single-dose administration of 200mg LCM as solution for infusion or tablet in healthy male subjects (arithmetic means) – SP645 and SP658

Trial	Drug Formulation	N	AUC(0-tz) (µg/ml/h)	Cmax (µg//ml)	Tmax (h)
			Mean (CV%)		Median (range)
SP645	Solution for infusion (15 min)	16	73.39 (17.4)	6.08(36.3)	0.25 (0.25-2.00)
	Tablet	16	74.91 (19.1)	4.88 (23.6)	0.75 (0.28-4.00)
SP658	Solution for infusion (30 min)	24	80.2 (23.9)	6.0 (28.0)	0.50 (0.50-2.00)

	Solution for infusion (60 min)	25	81.2 (24.8)	5.4 (22.5)	1.00 (1.00-3.00)
	Tablet	23	80.1 (24.0)	5.1 (27.9)	0.75 (0.25-4.00)

These studies also show that about 25% of the subjects had a Tmax in the infusion groups that were greater than the infusion duration. Although the actual Tmax's were longer than the infusion duration, but there were minimal differences in the mean Cmax values based on lacosamide concentrations at the end of infusion versus the actual Cmax as seen in the Table below:

Arithmetic mean ± standard deviation of LCM plasma concentrations at the end of the infusion and at t_{max}

Trial	Treatment	LCM concentration at the end of infusion (µg/mL)	C_{max} of LCM (µg/mL)
SP645	15min infusion	5.783 ± 2.599	6.075 ± 2.296
SP658	30min infusion	5.816 ± 1.623	5.955 ± 1.490
	60min infusion	5.297 ± 1.195	5.376 ± 1.095

These later tmax's could be the result of unbalanced distribution in the plasma. The differences observed are not clinically meaningful.

The 90% confidence intervals for the pharmacokinetic parameters from these studies are given below Although the sponsor has used AUC(0-tz) for calculating the 90% CIs, the values for AUC0-∞ are very close and similar to AUC(0-tz).

ANOVA results for the comparison "LCM as solution for infusion"/"LCM as tablet" – SP645 and SP658

Trial	Drug Formulation	Parameter	Point Estimate	90% Confidence Interval
SP645	Solution for infusion (15 min) /tablet	AUC(0-tz)	0.98	(0.96, 1.01)
		Cmax	1.20	(1.04, 1.38)
SP658	Solution for infusion 30 min)/tablet	AUC(0-tz)	1.00	(0.98, 1.01)
		Cmax	1.15	(1.07, 1.22)
	Solution for infusion (60 min)/tablet	AUC(0-tz)	1.00	(0.98, 1.02)
		Cmax	1.03	(0.96, 1.10)

Although on average the Cmax in the 15 minute infusion group was 20% higher in subjects on iv infusion, these subjects did not appear to have higher incidence of adverse events as

compared to the other subjects in the group. The reviewing Medical Officer will elaborate further on the safety aspects.

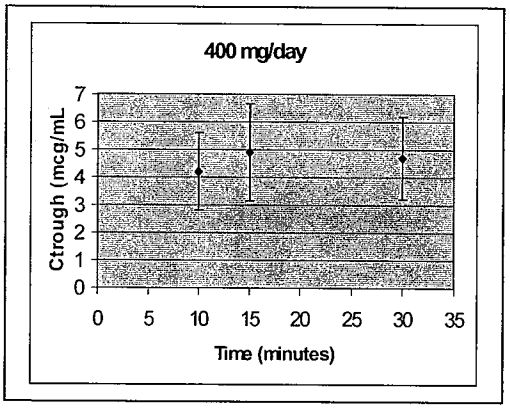
In addition to these bioequivalence studies the sponsor also evaluated the safety and tolerability of various infusion durations in patients with concomitant AEDs in two clinical studies SP757 and SP616. In study SP757 subjects were on stable 200-800 mg/day oral doses of lacosamide and were switched to the same iv dose for 2-5 days. Study SP616 was a crossover replacement study.

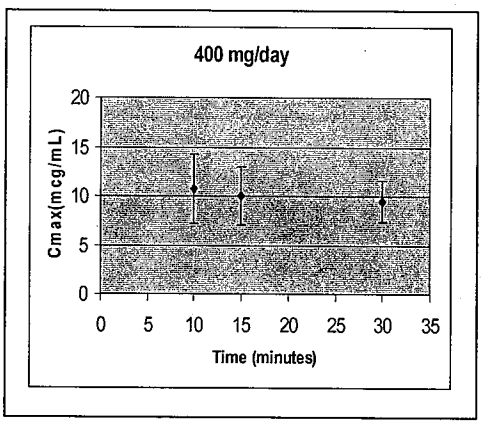
The number of subjects in the different infusion groups is given below.

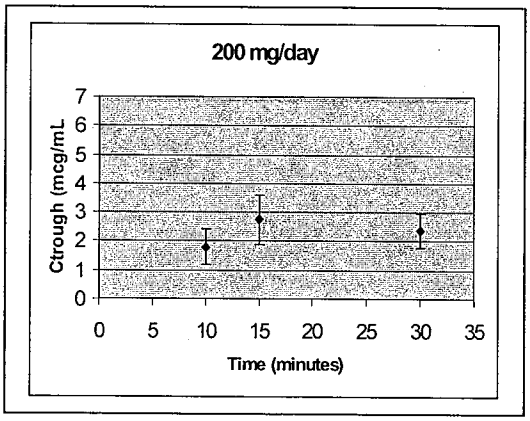
Sample size from the clinical studies:

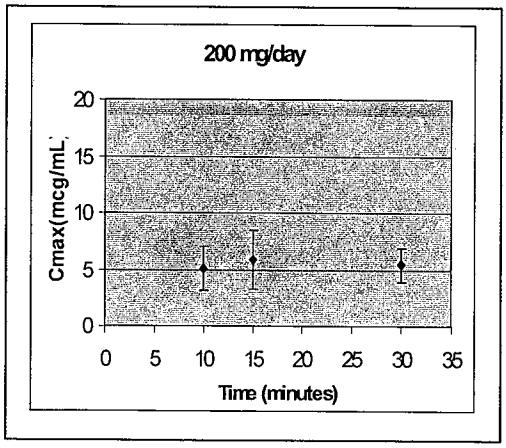
Infusion Duration	Study 757	Study 616
10 minutes	N=20	-
15 minutes	N=100	-
30 minutes	N=40	N=30
60 minutes	-	N=30

The sponsor also collected plasma samples at predose (Ctrough) and end of infusion (Cmax) at all doses for each infusion rate. The Ctrough and Cmax for the therapeutic doses of 200 and 400 mg/day are shown in the figures below. These figures show minimal differences in the Ctrough and/or Cmax values for the 10, 15 and 30 minute infusion durations for given dose. Sample size could be a factor for any observed differences.









It can be concluded from these figures that the 10, 15 and 30 minute infusions at a given dose gives comparable plasma concentrations of LCM.

The sponsor also compared the trough concentrations of the iv to the trough concentration on Day 1 of the oral lacosamide. After normalization for body weight and actual individual dose, LCM plasma concentrations(C_{trough}, C_{max}) were comparable across LCM doses. The ratios of geometric means including 90% confidence intervals (iv vs oral) of normalized C_{trough} for the 30-, 15-, and 10-minute infusion duration groups are presented in the following table.

Ratio of geometric means of normalized C_{trough} (µg/mL x kg/mg)Population:

Infusion duration (Cohort)	Treatment	n[a]	Comparison iv (test) vs oral (reference)	Ratio (%)	90% CI
30-minute	iv LCM /	28	Day 1 pm pre vs Day 1 am pre	95.4	(77.0, 118.2)
(Cohort A1)	oral LCM	28	Day 2 am pre vs Day 1 am pre	94.1	(76.0, 116.7)
		28	Day 2 pm pre vs Day 1 am pre	87.7	(70.7, 108.7)
15-minute	iv LCM /	84	Day 1 pm pre vs Day 1 am pre	89.2	(79.3, 100.4)
(Cohort B1	oral LCM	85	Day 2 am pre vs Day 1 am pre	92.5	(82.3, 104.0)
and B2)		84	Day 2 pm pre vs Day 1 am pre	86.1	(76.5, 97.0)
10-minute	iv LCM /	16	Day 1 pm pre vs Day 1 am pre	92.7	(68.0, 126.2)
(Cohort C)	oral LCM	16	Day 2 am pre vs Day 1 am pre	92.4	(67.8, 125.8)
		16	Day 2 pm pre vs Day 1 am pre	84.9	(62.4, 115.7)

CI=confidence interval; iv=intravenous; LCM=lacosamide

a Only subjects with a valid Day 1 am predose plasma value and a valid predose value for Day 1 pm, Day 2 am, and Day 2 pm were included.

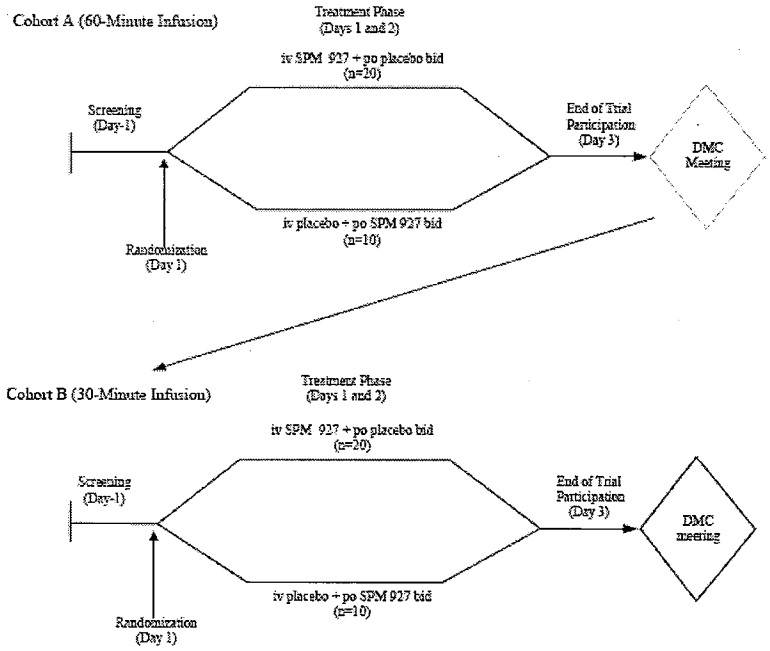
In general, the ratios of geometric means of normalized C_{trough} were similar across the various infusion duration groups and time points. The ratio of geometric means 85-95%, indicating that normalized C_{trough} plasma concentrations following iv LCM administration were comparable to normalized C_{trough} plasma concentrations after oral LCM administration. The lower limit of the 90% confidence interval were more on the lower side for the 10 and 30 minute infusions, probably due to the smaller sample size compared to the 15 minute infusion. These differences are within the between subject variability for LCM.

Therefore from a pharmacokinetic standpoint, although the definitive bioequivalence study showed that the 15 minute infusion showed a 20% higher Cmax compared to the oral LCM and failed the bioequivalence limit, the clinical relevance of this on the overall steady state concentrations may be minimal.

Also, the number of subjects on a 15 minute infusion is much higher than those on 30 or 60 minute infusion.

2.5.2 Does the pharmacokinetics of lacosamide differ when switched from oral to iv dosing?

In addition to the definitive bioequivalence studies, the sponsor evaluated the pharmacokinetics of lacosamide in the double blind, double dummy randomized trial with the 30 and 60 minute infusion groups. The schematic of the study design is given below. The results of this study are similar to that seen in the other studies that compare iv and oral administrations.



From Screening to End of Trial participation (Day -1, Day 1, Day 2, Day 3), subjects were maintained on a stable dose in accordance with current dosing from the open-label extension trial (SP615). Subjects entered the treatment phase (Day 1 and Day 2) under steady-state conditions. In both cohorts, all subjects received oral SPM 927 on Day -1. On Day 1 and Day 2, subjects received iv SPM 927 plus placebo tablets bid or iv placebo plus SPM 927 tablets bid, respectively. On the morning of Day 3 (=End of Trial phase), a single dose of oral SPM 927 was administered in accordance with each subjects's dosage regimen in the extension trial. Steady-state plasma concentrations of SPM 927 were determined on Day -1, Day 1, Day 2 and Day 3.

Pharmacokinetic parameters AUC(0-12), C_{max}, C_{min}, and $t_{1/2}$ were derived from concentration data of Day 2. Body weight and dose normalized pharmacokinetic parameters and the comparison between the 30 and 60 minute infusion groups is given in the following Table:

Normalized pharmacokinetic parameters on Day 2 and comparison between treatments (30- and 60-minute infusion vs oral)

Parameter (unit)	Cohort	Treatment		Comparison iv/oral	
		Oral SPM 927 / iv PBO	iv SPM 927 / oral PBO	Ratio (%)	90% CI
		Geometric mean±SD			
$AUC(0\text{-}12)_{norm}$ (µg/mL*h*kg/mg)	A	36.95±1.58 (N=10)	37.13±1.33 (N=17)	100.5	(74.1, 136.3)
	B	33.52±1.56 (N=11)	31.99±1.37 (N=15)	95.4	(70.4, 129.4)
$C_{max,norm}$ (µg/mL*kg/mg)	A	4.35±1.53 (N=10)	4.85±1.31 (N=17)	111.4	(84.6, 146.7)
	B	3.74±1.49 (N=11)	4.42±1.30 (N=15)	118.1	(89.7, 155.6)
$C_{min,norm}$ (µg/mL*kg/mg)	A	2.05±1.71 (N=10)	1.90±1.60 (N=17)	92.7	(62.7, 137.0)
	B	1.93±1.66 (N=11)	1.72±1.48 (N=15)	89.3	(60.4, 132.0)

CI= confidence interval; iv = intravenous; PBO = placebo; SD = standard deviation
Cohort A: 60-minute iv infusion; Cohort B: 30-minute iv infusion

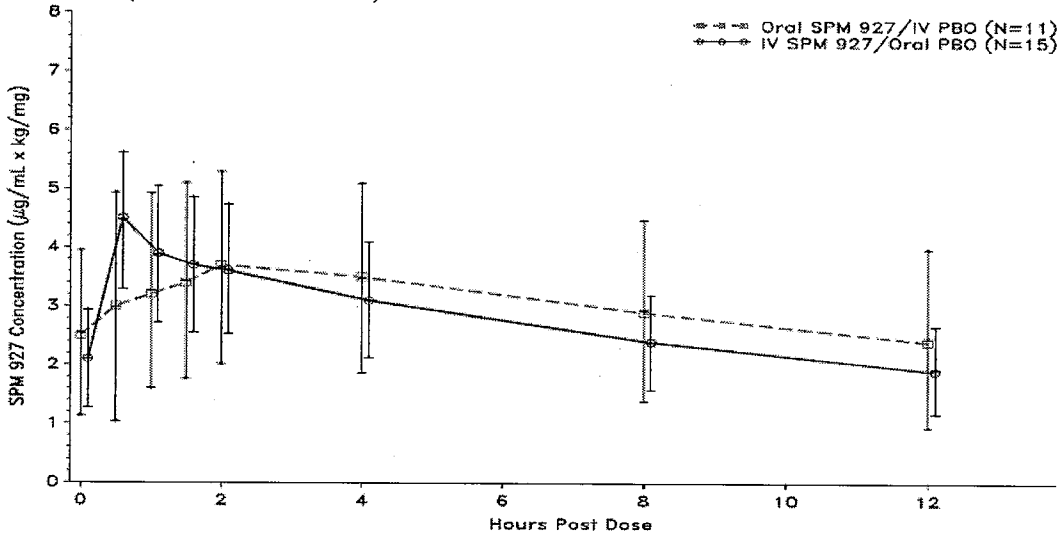
- The bioavailability of LCM after iv treatment for both the 60 and the 30-minute infusion was comparable to that after oral treatment. Ratios iv/oral for $AUC(0\text{-}12)_{norm}$ were 95-100%, although the 90% confidence intervals were outside the acceptable range. [note: BE in definitive BE studies].

- Values of $C_{max,norm}$ were slightly elevated after iv treatment compared to oral treatment. This is reflected in ratios iv/oral of 111-118% for $C_{max,norm}$. These values are similar to that seen with the definitive bioequivalence study. These higher concentrations are seen within the first 1.75 hours of dosing.

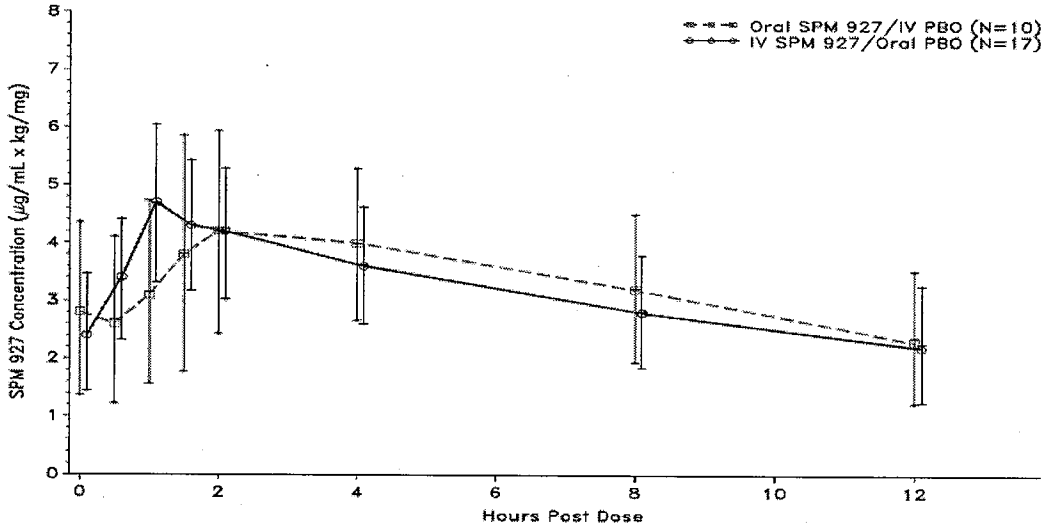
- Values of $C_{min,norm}$ were slightly decreased after iv treatment which is reflected in ratios iv/oral of approximately 90%, also as seen in other studies.

The mean normalized concentration time profile for the 30 and 60 minute infusions are displayed in the following figures:

Mean SPM 927 plasma concentration versus time on Day 2 normalized by body weight and dose (30 minute infusion)



Mean SPM 927 plasma concentration versus time on Day 2 normalized by body weight and dose (60 minute infusion)



The t_{max} was shorter after iv administration of SPM 927 compared to oral administration. After oral administration of SPM 927, t_{max} was reached between 1.5 and 4 hours after administration in the majority of subjects. The Cmin was lower with the iv administration although within the variability seen with the oral administration. The concentrations within the first 1.75 hours after dosing were higher after iv administration.

Unless safety and tolerability is a concern, these differences may not be clinically meaningful.

2.5.3 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Lacosamide is a BCS Class I drug product. For additional details refer to IND review.

2.5.4. Is the proposed to-be-marketed formulation of lacosamide bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

Tablets:

The proposed to-be-marketed or commercial formulation (tablet ——)was not used in any clinical trials in this submission. The various formulations used in the clinical trials were the capsules hand filled with pure drug, capsules filled with powder blend and film coated tablets. The sponsor has requested a biowaiver to conduct bioequivalence studies between the clinical trial and commercial formulations based on BCS classification I. This waiver request is evaluated by the review Chemist. For reference, the formulations used in various studies is summarized in the following Table:

b(4)

Trial code	Aim of trial	Dose	Formulation
SP835	Phase 1 (tolerability, PK)	100 mg/200 mg	Capsules hand-filled with pure drug substance
SP836	Phase 1 (tolerability, PK)	100 mg/200 mg	
SP586	Phase 2 (epilepsy)	50 mg/100mg/200mg	
SP587	Phase 1 (tolerance)	100 mg	Capsules filled with powder blend
SP588	Phase 1 (tolerance)	100 mg	
SP598	Phase 2 (epilepsy)	50 mg/100 mg/200 mg	
SP599	Phase 1 (interaction study)	100 mg	
SP601	Phase 1 (interaction study)	100 mg	
SP602	Phase 1 (interaction study)	100 mg	
SP603	Phase 1 (interaction study)	100 mg	
SP611	Phase 2 (neuropathic pain)	100 mg	
SP618	Phase 1 (interaction study)	100 mg	
SP600	Phase 1 (bioavailability)	100 mg	Film-coated tablets (clinical trial formulation)
SP620	Phase 1 (different ages and genders)	100 mg	
SP640	Phase 1 (QT-trial)	50 mg/100 mg	
SP641	Phase 1 (renal impairment)	100 mg	
SP642	Phase 1 (hepatic impairment)	100 mg	
SP643	Phase 1 (metabolism, bioequivalence)	100 mg	
		20mg/mL i.v. solution	
SP644	Phase 1 (interaction study)	100 mg	
SP645	Phase 1 (metabolism, bioequivalence)	100 mg	
		20mg/mL i.v. solution	
SP657	Phase 1 (bioequivalence)	100 mg	
		Syrup 10mg/ mL	
SP658	Phase 1 (bioequivalence)	10mg/mL i.v. solution	
		100 mg	
SP660	Phase 1 (interaction study)	100 mg	
SP661	Phase 1 (different ethnic groups)	100 mg	
SP863	Phase 1 (interaction study)	100 mg	
SP903	Phase 1 (abuse liability)	100 mg	
SP607	Phase 2 (epilepsy)	50 mg/100 mg	
SP615	Phase 2 (epilepsy)	50 mg/100 mg	
SP616	Phase 2 (epilepsy)	10mg/mL i.v. solution	
		50 mg/100 mg	
SP667	Phase 2 (epilepsy)	50 mg/100 mg	
SP754	Phase 3 (epilepsy)	50 mg/100 mg	
SP755	Phase 3 (epilepsy)	50 mg/100 mg	
SP756	Phase 3 (epilepsy)	50 mg/100 mg	
SP757	Phase 3 (epilepsy)	10mg/mL i.v. solution	
SP774	Phase 3 (epilepsy)	50 mg/100 mg	

The overview of the different formulations is also given in the following Table

Overview on the different formulations (exemplary for a 100 mg dosage strength)

Ingredient	Capsule [mg]	Capsule [mg]	Clinical trial formulation [mg]	Commercial formulation (proportional) [mg]
Lacosamide	100.00	100.00	100.00	100.00
Hypromellose				
Hydroxypropyl cellulose				
Cellulose, microcrystalline				
Crospovidone				
Magnesium stearate				

b(4)

b(4)

Please refer to chemistry review for further details.

b(4)

b(4)

For solution for infusion:

The commercial formulation (10 mg/mL) has been used in the bioequivalence study SP 658 (30 and 60 minutes infusion duration versus Tablets) and the Phase 2 and 3 studies (SP 616 and SP757, which studied the 10, 15, 30 and 60 minute infusions) that support safety and tolerability of the drug product. The initial metabolism studies and the 15 minute infusion study SP645 were conducted with a higher strength of 20 mg/mL as can be seen in the Table below:

Lacosamide solution for infusion used in clinical trials

Trial code	Aim of trial	Dose
SP643	Phase 1 (metabolism, bioequivalence)	100 mg 20 mg/mL i.v. solution
SP645	Phase 1 (metabolism, bioequivalence)	100 mg 20 mg/mL i.v. solution
SP658	Phase 1 (bioequivalence)	10 mg/mL i.v. solution 100 mg
SP616	Phase 2	10 mg/mL i.v. solution 50 mg/100 mg
SP757	Phase 3	10 mg/mL i.v. solution

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of lacosamide in relation to meals or meal types?

There was no effect of food on the bioavailability of lacosamide (3x100 mg). Food had no effect on Cmax or AUC. However, median Tmax was ~0.5 hour delayed under fed conditions. For additional details please refer to the review by Dr Fadiran.
Food effect study has not been studied with the highest strength.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation methods for lacosamide and SPM12809 in plasma and urine are reviewed by Drs Fadiran and Zhang. Please refer to their review for details.

For the quantification of LCM and its main metabolite SPM 12809 in clinical trials, various liquid chromatography-mass spectrometry (LC-MS) methods were developed and validated using ——— internal standards to provide appropriate accuracies and robustness. A complete list of analytical methods and their use in Clinical Pharmacology studies is provided in the following Table. b(4)

In general, all bioanalytical methods were accurate, robust, and reliable and adequately determined the concentrations of the compounds of interest. The long-term stability in frozen plasma and urine is appropriate to cover the time between sample collection and analysis. Refer to individual study reviews for the performance outcome of each analytical method.

3.0 DETAILED LABELING RECOMMENDATION

31 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.1 APPENDIX I

4.1.1 INDIVIDUAL STUDY REVIEW

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

BE BETWEEN TABLETS AND SOLUTION FOR INFUSION

Study SP645: Randomized, open-label, single-dose, 2-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in healthy male subjects

In clinical practice the need may arise for a short-term replacement of oral therapy with lacosamide by therapy via an intravenous (iv) route, e.g., as pre- and postsurgery treatment. Hence, bioequivalence between the two routes of administration is desirable.

Objectives:

- to evaluate the bioequivalence of an 15 minute intravenous (iv) infusion of lacosamide (SPM 927) in comparison to a tablet in healthy subjects, and
- to evaluate the safety and tolerability of both formulations.

The study design is as follows:

Trial Site	/ / / / / b(4)
Study Design	This was an open-label, single-dose, 2-way crossover trial in which healthy subjects
Study Population	N=24 Healthy subjects randomized and N=16 valid for PK analysis Age: 21-45 years (mean 32.6 years) Gender: All males Weight: 50-101 kg (mean 77.3 kg) Race: All White
Treatment Group	Treatment A (test): 200mg lacosamide as iv infusion over 15 minutes, single dose Treatment B (Ref): 200mg lacosamide as oral tablet (2 tablets of 100mg) , single dose
Dosage and Administration	Subjects were randomly assigned to either treatment sequence AB or BA. Treatment A consisted of a single iv infusion of 200mg lacosamide in 20mL saline over 15 minutes, which was administered in the morning of Day 1. The iv solution was prepared from a stock solution by diluting with isotonic sodium chloride immediately before administration. Treatment B consisted of a single oral dose of 200mg lacosamide, which was administered as 2 tablets of 100mg in the morning of Day 1. Subjects were hospitalized during the 2 treatment periods (from the afternoon of Day -1, the day before administration of the trial medication, until the last examinations of Day 4) Diet: On Day 1 of each treatment period, subjects were fasting for at least 10 hours before the administration of trial medication as well as

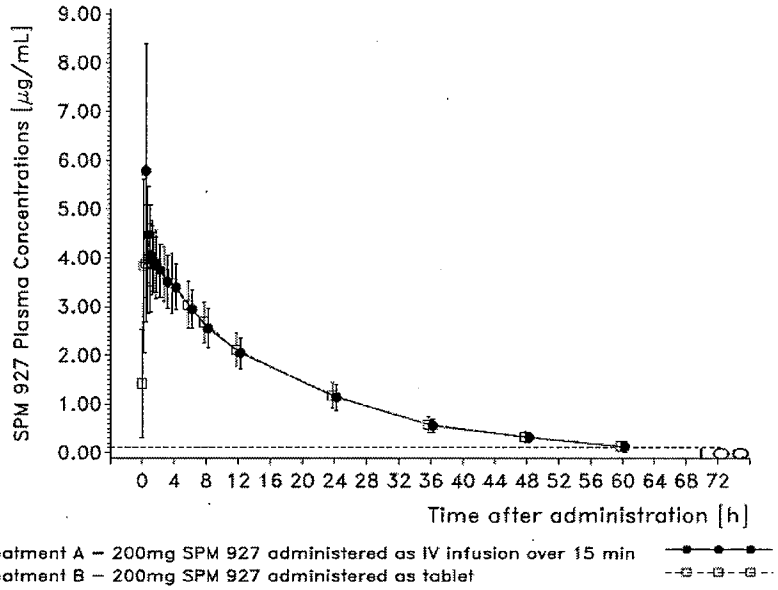
	until approximately 4 hours after dosing (start of infusion or intake of tablet) when a lunch was served. Only beverages without alcohol, caffeine, quinine, or grapefruit were served. Subjects were not allowed to smoke on Day 1 of each treatment period. Washout: Wash-Out Phase of at least 7 days between treatments
Sampling: Blood	For Lacosamide: Day1: Predose (0) and postdose at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours
Urine	none
Feces	none
Analysis	Method: LC/MS/MS method in plasma Lower Limits of Quantitation: Plasma Lacosamide 0.10336 µg/mL Plasma: Linear Range: 0.10-20 µg/ml in plasma Quality control concentrations 0.220, 2.5, 15 µg/ml Inter-day precision: < 4.71 %CV Inter-day accuracy: -1.01-2.52 % bias
PK Assessment	Lacosamide in plasma Primary PK parameters were: • AUC(0-tz) and Cmax of lacosamide in plasma. Secondary PK parameters were: • AUC(0-∞), t1/2, tmax of lacosamide
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma:

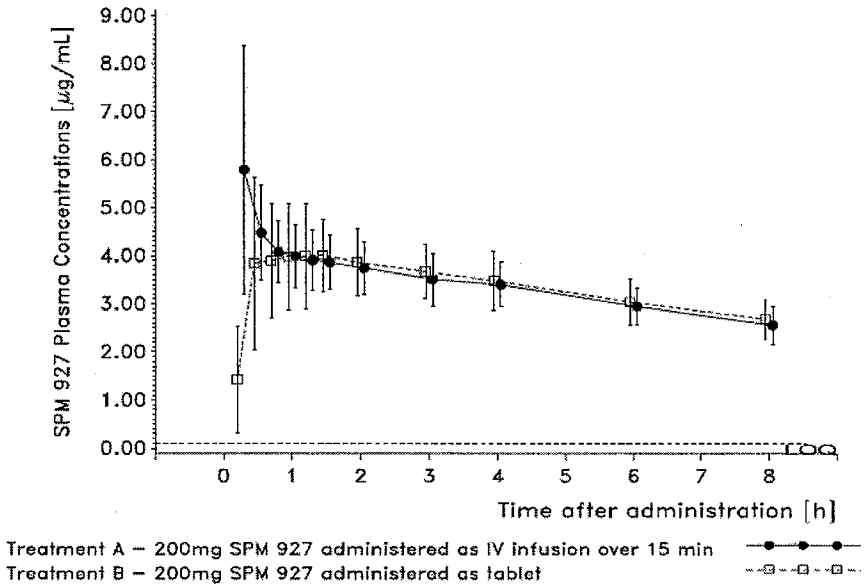
Mean plasma concentrations after administration of 200mg lacosamide as 15-minute iv infusion (Treatment A) or as tablet (Treatment B) are shown in the following figure:

Mean plasma concentrations after iv (Treatment A) and po (Treatment B) administration of 200mg lacosamide (0-72 hours)



The figure below shows the mean plasma concentrations between 0 to 8 hours after iv and po administration of 200mg lacosamide.

Mean plasma concentrations after iv (Treatment A) and po (Treatment B) administration of 200mg lacosamide (0-8 hours)



The median t_{max} was 0.25 hours after 15-minute iv infusion and 0.75 hours after po

administration.

The table below summarizes the primary and secondary PK parameters of lacosamide after single iv and po administration.

Single-dose pharmacokinetics of lacosamide after iv and po administration

Parameter	200mg lacosamide iv (N=16)	200mg lacosamide po (N=16)
$AUC_{(0\text{-}tz)}$ [a] (h*µg/mL)	73.39±13.64	74.91±14.68
$AUC_{(0\text{-}\infty)}$ [a] (h*µg/mL)	76.46±13.93	77.73±14.79
C_{max} [a] (µg/mL)	6.08±2.30	4.88±1.10
t_{max} [b] (h)	0.25 (0.25-2)	0.75 (0.28-4)
$t_{1/2}$ [b] (h)	12.61 (10.78-16.09)	12.96 (10.09-16.18)

[a] Arithmetic mean±SD

[b] Median (range)

Point estimates and corresponding 90% CIs for the comparison "Treatment A"/"Treatment B" are presented in the table below.

ANOVA results: Test for bioequivalence between po and iv administration of lacosamide

Parameter	Ratio Treatment A/B	90% confidence interval
$AUC_{(0\text{-}tz)}$	0.98	(0.96, 1.01)
C_{max}	1.20	(1.04, 1.38)

Treatment key: Treatment A=iv administration; Treatment B=po administration

The 90% CI for $AUC_{(0\text{-}tz)}$ for the comparison "15-minute iv infusion"/"po administration" was within the generally accepted bioequivalence range (0.8, 1.25).

The 90% CI for C_{max} for the comparison "15-minute iv infusion"/"po administration" exceeded the upper boundary of the bioequivalence range (0.8, 1.25).

Safety:

The most frequently reported AEs in this trial were dizziness and paraesthesia oral. The incidence of TEAEs was higher after iv administration (21 TEAEs in 10 subjects) than after po administration (16 TEAEs in 7 subjects).

Conclusions:

- The 90% CI for $AUC_{(0\text{-}tz)}$ for the comparison "15-minute iv infusion"/"po administration" was within the generally accepted bioequivalence range (0.8, 1.25).

The PK characteristics of lacosamide in plasma are consistent with those obtained in previous trials and confirm the high absolute bioavailability of the tablet (approximately 100%)

- The 90% CI for C_{max} for the comparison "15-minute iv infusion"/"po administration" slightly exceeded the upper boundary of the bioequivalence range (0.8, 1.25). It was known from earlier trials that C_{max} occurred about 1 to 2 hours after administration of the tablet, a somewhat higher maximum concentration after a 15-minute iv infusion compared to po administration was expected, since the Cmax would be at the end of infusion. The clinical relevance of this with regards to safety would be evaluated by the Medical Reviewer.
- Therefore, bioequivalence of a 15-minute iv infusion of lacosamide and the tablet could not be shown in this trial.
- The median t_{max} was 0.25 hours after 15-minute iv infusion and 0.75 hours after po administration.
- The median $t_{1/2}$ was approximately 13 hours for both routes of administration.

Reviewer's Comment:

Looking at the individual data it did not appear that subjects that had a higher Cmax had any additional adverse events. In fact some subjects with high Cmax did not show any adverse events compared to the subjects that had lower Cmax. For example subjects 80009, 80011, 80012 and 81001 had Cmax in the range of 8.04-11.25 mcg/mL after IV administration, but these subjects did not have any adverse events that were different from the general population.

Study SP658: Randomized, open-label, single-dose, 3-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in 24 healthy male subjects

In clinical practice the need may arise for a short-term replacement of oral therapy with lacosamide by therapy via an intravenous (iv) route, e.g., as pre- and postsurgery treatment. Hence, bioequivalence between the two dosage forms is desirable. The 15 minute infusion trial has failed to show bioequivalency.

Objectives:

- Primary objective of this trial is to evaluate the equivalence of an intravenous infusion (duration 30 and 60 minutes) of SPM 927 (lacosamide) in comparison to an oral tablet in healthy subjects.

- Secondary objectives are the safety and tolerability of lacosamide after intravenous and oral administration.

The study design is as follows:

Trial Site	[redacted] b(4)
Study Design	This was an open-label, single-dose, 3-way crossover trial in which healthy subjects received the following 3 treatments in a randomized order
Study Population	N=27 Healthy subjects randomized and N=22 valid for analysis Age: 18-45 years (mean 31 years) Gender: All males Weight: 63-90 kg (mean 73 kg) Race: All White
Treatment Group	Treatment A (test 1): 200mg lacosamide as iv infusion over 30 minutes, single dose Treatment B (test 2): 200mg lacosamide as iv infusion over 60 minutes, single dose Treatment C (reference): 200mg lacosamide as oral tablet (2 tablets of 100mg) , single dose
Dosage and Administration	• A single dose of 200mg lacosamide solution for infusion was administered intravenously over 30 minutes (Treatment A) or 60 minutes (Treatment B). • A single dose of 200mg lacosamide was administered orally as 2 tablets of 100mg (Treatment C). There were 3 treatment periods (single doses); subjects were hospitalized for 4 days in each period. For Treatments A and B, approximately 240mL tap water was given immediately before the start of the infusion. For Treatment C, 2 tablets, each containing 100mg lacosamide, were administered orally with approximately 240mL tap water. Subjects had to stay in bed (semi-recumbent or lying down) for at least

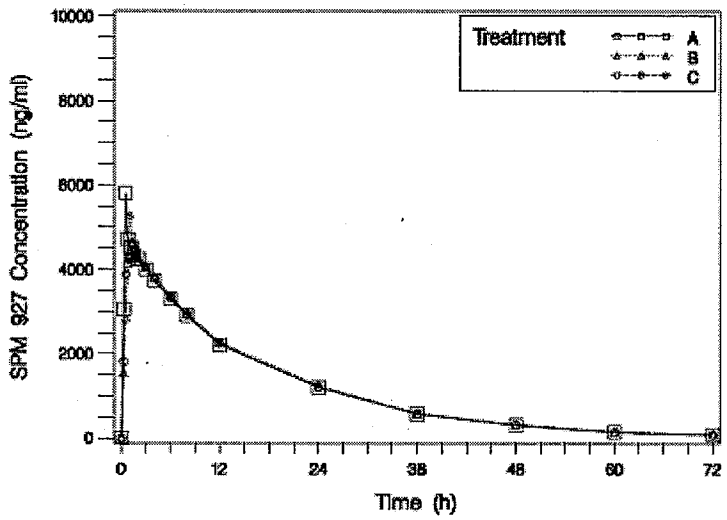
	2 hours after oral administration of lacosamide (Treatment C) as well as after the end of the infusions (Treatments A and B). IV administration: lacosamide solution for infusion (solution of 200mg lacosamide in 20mL). Batch number of bulk product: 20030154 PO administration: 100mg film-coated lacosamide tablets; Batch number of bulk product: 20030154 Lacosamide was supplied by SCHWARZ BIOSCIENCES GmbH, Monheim, Germany. Diet: On Day 1 of each treatment period, subjects were fasting for at least 10 hours before the administration of trial medication as well as until approximately 4 hours after dosing (start of infusion or intake of tablet) when a lunch was served. Only beverages without alcohol, caffeine, quinine, or grapefruit were served. Subjects were not allowed to smoke on Day 1 of each treatment period. Washout: Wash-Out Phase of at least 7 days between treatments
Sampling: Blood	For Lacosamide: Day1: Predose (0) and postdose at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours
Urine	none
Feces	none
Analysis	Method: LC/MS/MS method in plasma Lower Limits of Quantitation: Plasma Lacosamide 10 ng/ml Plasma: Linear Range: 10-10000 ng/ml in plasma for both moieties Quality control concentrations 40, 1000, 8000 ng/ml Inter-day precision: < 4.0 %CV Inter-day accuracy: 99.6-101.5% of the nominal concentration
PK Assessment	Lacosamide and SPM 12809 in plasma Primary PK parameters were: • AUC(0-tz) and Cmax of lacosamide in plasma. Secondary PK parameters were: • AUC(0-∞), t1/2, tmax, and frel of lacosamide
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma:

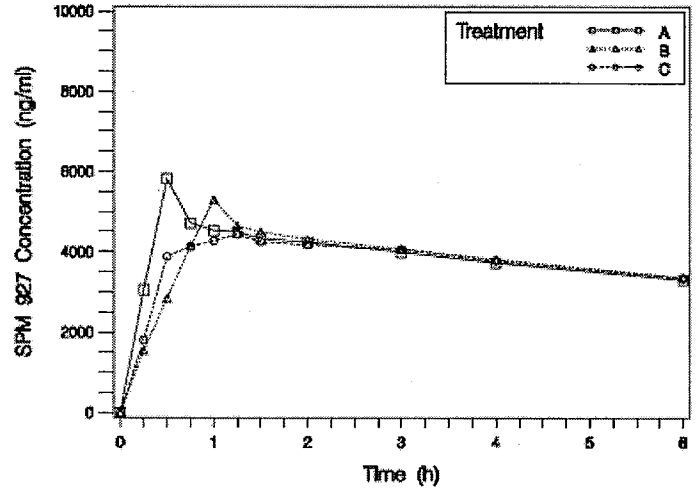
The mean plasma concentration-time curves of lacosamide for the Treatments A (200mg lacosamide, 30min iv), B (200mg lacosamide, 60min iv), and C (200mg lacosamide, oral) are shown in the figure below.

Mean plasma concentration-time curves of lacosamide for Treatments A (N=24), B (N=25), and C (N=23) – 0-72 hours



The plasma concentration-time profiles of Treatments A, B, and C between 0 and 6 hours after administration are shown in the figure below to provide a more detailed picture about the absorption phase and the times to reach maximum mean concentrations.

Mean plasma concentration-time curves of lacosamide for Treatments A (N=24), B (N=25), and C (N=23) – 0-6 hours



Summary statistics of the primary and secondary PK parameters after single-dose administration of 200mg lacosamide are presented in the following table.

Pharmacokinetic parameters after intravenous or oral administration of 200mg lacosamide

Parameter (Unit)	Treatment		
	A (N=24)	B (N=25)	C (N=23)
$AUC(0\text{-}t_z)$[a] ($\mu g/mL*h$)	80.2±16.6 (35.5-112.4)	81.2±17.6 (35.1-116.2)	80.1±17.6 (38.4-123.4)
C_{max}[a] ($\mu g/mL$)	6.0±1.5 (2.8-8.5)	5.4±1.1 (2.8-7.2)	5.1±1.4 (2.4-8.5)
$AUC(0\text{-}\infty)$[a] ($\mu g/mL*h$)	81.8±17.7 (35.9-118.5)	82.8±18.8 (35.5-122.9)	81.7±19.0 (38.9-131.4)
t_{max}[b] (h)	0.50 (0.50-2.00)	1.00 (1.00-3.00)	0.75 (0.25-4.00)
$t_{1/2}$[b] (h)	11.4 (9.3-17.0)	11.3 (9.5-17.2)	11.2 (9.3-18.0)
λ_z[b] (1/h)	0.0610 (0.0408-0.0749)	0.0614 (0.0404-0.0730)	0.0622 (0.0385-0.0746)
CL_{tot}[a,c] (L/h)	2.59±0.76 (1.69-5.57)	2.57±0.78 (1.63-5.64)	2.59±0.72 (1.52-5.14)

Treatment key: A=iv 30-minute infusion; B=iv 60-minute infusion; C=oral administration

[a] Arithmetic mean±standard deviation (range)

[b] Median (range)

[c] Clearance of lacosamide is given as total clearance (CL_{tot}) after iv administration and as total apparent clearance (CL_{tot}/f) after oral administration (see list of PK parameters in

Mean values for $AUC(0\text{-}t_z)$ including SD and range were similar for all 3 treatments (mean values: 80.1-81.2µg/mL*h). The same is valid for $AUC(0\text{-}\infty)$. Since the AUC was the same after oral and iv administration, this trial indicates that the oral formulation of lacosamide has an absolute bioavailability of approximately 100%.

Additionally, point estimates and 90% CIs for the ratios A/C and B/C, comparing the 30-minute infusion with the oral formulation and the 60-minute infusion with the oral formulation, respectively, were calculated by re-transforming the logarithmic data using the intra-individual SD of the ANOVA. The ratios for the primary PK parameters $AUC(0\text{-}t_z)$ and C_{max} and the 90% CIs are presented in the table below.

Test for bioequivalence: Ratios and 90% confidence intervals for primary pharmacokinetic parameters

Parameter	Ratio 90% Confidence Interval	
	A/C	B/C
AUC(0-tz)	99.4% (97.6, 101.3)	99.7% (97.9, 101.6)
Cmax	114.8% (107.7, 122.4)	102.9% (96.5, 109.7)

The results indicate that point estimates and 90% CIs of the ratios A/C and B/C for AUC(0-t_z) and C_{max} were within the generally accepted range for bioequivalence trials of (80%, 125%).

Treatment ratios A/C and B/C for AUC(0-t_z) of approximately 1.00 (ie, a relative bioavailability of 100%) indicate the same bioavailability for lacosamide as intravenously administered solution for infusion (over 30 or 60 minutes) compared to the oral formulation. Regarding C_{max}, the treatment ratio A/C is slightly increased which indicates that C_{max} is slightly higher after iv administration as 30-minute infusion. This finding of a slightly higher C_{max} was expected for the 30-minute infusion, as this results from the higher rate of drug input into the systemic circulation.

Adverse Events:

The adverse events in the three treatment groups is shown in the following Table:

Numbers (and percentages) of subjects reporting at least 1 treatment-emergent adverse event

WHO-ART Body System/ Coded Term	Treatment			Total
	A (30min iv)	B (60min iv)	C (oral)	
	(N=24)	(N=25)	(N=23)	(N=27)
	n (%)			
Any body system	**8 (33)**	**7 (28)**	**5 (22)**	**13 (48)**
Body as a whole – general disorders	**4 (17)**	**3 (12)**	**3 (13)**	**5 (19)**
Tiredness	3 (13)	2 (8)	3 (13)	4 (15)
Feeling of warmth	1 (4)	1 (4)	0	1 (4)
Central and peripheral nervous system disorders	**2 (8)**	**4 (16)**	**2 (9)**	**6 (22)**
Dizziness	0	1 (4)	1 (4)	2 (7)
Numbness localized	1 (4)	1 (4)	0	2 (7)
Paraesthesia circumoral	0	1 (4)	2 (9)	2 (7)
Headache	0	1 (4)	0	1 (4)
Muscle stiffness	1 (4)	0	0	1 (4)
Gastro-intestinal system disorders	**1 (4)**	**0**	**0**	**1 (4)**
Diarrhea	1 (4)	0	0	1 (4)
Musculoskeletal system disorders	**1 (4)**	**0**	**0**	**1 (4)**
Myalgia	1 (4)	0	0	1 (4)
Psychiatric disorders	**0**	**1 (4)**	**0**	**1 (4)**
Anxiety	0	1 (4)	0	1 (4)
Nightmares	0	1 (4)	0	1 (4)
Respiratory system disorders	**2 (8)**	**2 (8)**	**0**	**4 (15)**
Throat sore	1 (4)	1 (4)	0	2 (7)
Upper respiratory tract infection	1 (4)	1 (4)	0	2 (7)
Skin and appendage disorders	**1 (4)**	**0**	**0**	**1 (4)**
Urticaria	1 (4)	0	0	1 (4)

Data source: Table 4.1

The adverse events were generally comparable between treatment groups. The most common adverse event was tiredness.

Conclusions:

In summary, this trial indicates that the pharmacokinetics of lacosamide are similar when lacosamide is given as 30-minute infusion, 60-minute infusion, or as tablet and that the

lacosamide solution for infusion administered over 30 or 60 minutes is bioequivalent to the oral tablet.

REPLACEMENT OF ORAL WITH SOLUTION FOR INFUSION

Study SP757: A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization

The safety aspects from this study will be reviewed by the Medical Officer. The sponsor also collected PK data in this study which will be reviewed by this reviewer.

Objectives:

The objectives of this trial were to evaluate the safety and tolerability of lacosamide (LCM; SPM 927) when given as intravenous (iv) infusions in subjects who were receiving oral LCM in addition to up to 3 concomitant antiepileptic drugs (AEDs) for partial seizures with or without secondary generalization.

The study design is as follows:

Trial Site	Thirty-three sites were activated in the United States of America (USA) and 4 countries in Europe (Czech Republic, Germany, Lithuania, and Sweden). Twenty-six of these sites screened and enrolled at least 1 subject.
Study Design	This multicenter, open-label, inpatient trial was conducted at 26 enrolling sites in the USA and Europe participating in an open-label extension trial of oral LCM (SP615, SP756, or SP774). A total of 160 subjects were enrolled into 1 of 5 possible cohorts in this trial. This trial was designed to identify the appropriate infusion duration(s) for LCM and provide the data to support the safety of that infusion rate. Execution of this trial design resulted in the administration of LCM at progressively faster infusion durations under the direction of a Data Monitoring Committee (DMC). The subjects were maintained on the stable dose (100 to 300mg twice daily, i.e. 200 to 600 mg/day) that they had last received in the open-label extension trial. In Cohorts A2 and B2, subjects receiving 700mg/day or 800mg/day were to be allowed to enter the trial only after review of the safety data from the first 3 cohorts. The Treatment Phase was 2 to 5 days. Subjects entered into a 1-day Screening Phase followed by a Treatment Phase during which subjects received iv LCM infused over 10, 15, or 30 minutes twice daily (depending on cohort assignment). For Cohort A1, the Treatment Phase was 2 days. However, in all subsequent cohorts, subjects had the option to receive inpatient iv dosing of LCM for 2 to 5 days. The dose of iv LCM was the same as the subject's current daily dose in the open-label extension trial of oral LCM. End of Trial Phase assessments were performed the day after the Treatment Phase was completed, after which subjects continued in the open-label extension trial (SP615, SP756, or SP774) where they resumed dosing

	with oral LCM as stipulated in that protocol.
Study Population	N=160 patients
Treatment Group	10 min infusion: N=20 15 minute infusion: N=100 30 minute infusion: N=40
Dosage and Administration	On Day -1, oral LCM tablets were administered in accordance with each subject's LCM dosage regimen in the open-label extension trial (SP615, SP756, or SP774). The tablets were taken from the open-label extension supply. Batch Numbers: 075704120001, 075705060002, 075705060003, 075704120003, 075705060005, 075704120004, 075705060004, and 075705110003 During the Treatment Phase, trial medication (iv LCM solution) was administered twice daily at 12-hour intervals, once in the morning and once in the evening. Subjects remained on the same stable dose that they had received during their previous 2 weeks in the open-label extension trial (100 to 400mg bid). Asymmetrical dosing (ie, taking a different dose morning vs evening) was not permitted. Subjects on 700mg/day or 800mg/day were allowed to enter the trial only after review of the safety data from the first 3 cohorts. Dietary regimen Throughout the trial, non-alcoholic beverages may have been served. The subjects were not allowed to consume alcohol during the trial. Breakfast, lunch, snacks, and evening meals were provided by the site.
Sampling: Blood	Blood samples were collected for analysis of trough concentration (Ctrough) and measured maximum concentration (end of infusion) (Cmax) for LCM as well as the O-desmethyl-metabolite of LCM (SPM 12809). In addition, predose concentrations of concomitant AEDs were determined at Day -1.
Urine	none
Feces	none
Analysis	Method: LC/MS/MS method in plasma Lower Limits of Quantitation: Plasma Lacosamide 0.01 µg/mL SPM 12809 0.01 µg/mL Plasma: Linear Range in plasma 0.01-10 µg /ml for both Quality control concentrations : 0.02, 2 and 10 µg /ml Inter-day precision: < 3.4%CV for LCM and 3.8% for SPM 12809 Inter-day accuracy: -100.9-101.9 fro LCM and 100.7-102.4 for SPM