Table 1: Pharmacokinetic parameters of LCM following single oral administrations of 400, 600, and 800mg LCM in healthy male subjects.

Parameter (unit)	Statistic	400mg N=12	600mg N=12	800mg 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

CV=coefficient of variation; LCM=lacosamide; SD=standard deviation

a In 3 of the 12 subjects receiving LCM in the 800mg group, the dose was reduced in Treatment Period 3. Two of the 3 subjects received 300mg and 1 subject received 500mg LCM instead of 800mg.

b The geometric CV(%) was calculated additionally and is not reported in the SP587 Clinical Trial Report.

Table 2: Summary of Urinary PK

	Dose SPM927		
	400 mg	600 mg	800 mg
Hours after dosing	N=12[a]	N=12[b]	N=9
0-4	19.2 ± 6.3	30.5 ± 12.5	44.0 ± 20.0
4-8	15.6 ± 5.2	34.6 ± 13.2	54.6 ± 19.0
8-12	14.0 ± 5.4	25.6 ±11.0	22.4 ± 6.0
12-24	17.3 ± 5.5	27.8 ± 11.9	41.0 ± 15.1
24-36	12.7 ± 4.4	17.5 ± 6.8	22.4 ± 9.8
36-48	6.6 ± 2.7	8.4 ± 5.0	13.4 ± 6.9
Total (0-48)	84.9 ± 10.7	144.4 ± 27.5	198.5 ± 51.6
Renal clearance [l/h] (0-24)	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.3

a 8-12 h after dosing N = 11

b 36-48 h after dosing N = 11

Data source: Section 13.2, Table 10.2.7

Comments: AUC(0-tz), AUC(0-∞), and Cmax as well as Ae increased proportionally with the administered dose.

Other PK parameters (tmax, t1/2, total body clearance [CL/f], and renal clearance [CLrenal]) of LCM were unchanged at the different doses.

The dose-proportional increase of AUC(0-∞) and Cmax was demonstrated for AUC and Cmax of LCM with the dose between 400 mg and 800 mg.

PK conclusion: Lacosamide was absorbed with a tmax occurring between 1.0 and 4.0 hours after dosing and a terminal half-life of approximately 13 hours. AUC and Cmax of LCM increased proportionally with the dose between 400 mg and 800 mg.

4.2.2.2 Dose Proportionality Studies—Multiple Doses

4.2.2.2.1 Study SP836: Double-blind, randomized, placebo-controlled, parallel group, 7-day oral ascending dose study to determine the tolerability and pharmacokinetic profile of SPM 927

Study Type: Multiple dose study.

b(4)

Clinical Investigator: [redacted]

Objectives: The primary objective was to investigate the safety and tolerability of multiple oral doses of SPM 927 in healthy male subjects. The secondary objective was to determine the PK profile of SPM 927 following multiple oral dose administration.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group Phase 1 trial in healthy male subjects using SPM 927 capsules hand-filled with the pure drug substance. Twenty-one subjects were randomized to 3 groups of 7 subjects. In each group, 6 subjects were randomized to 100 mg SPM 927 once daily on 7 consecutive days, 200mg once daily on 7 consecutive days, or 200 mg twice daily on 6 consecutive days and in addition once daily on Day 7. One subject in each group was randomized to placebo.

Blood sampling times: Samples (7 ml) were collected at the following times:

Interval	Subjects 1-7 (100 mg od [Group 1] Subjects 8-14 (200 mg od [Group 2])	Subjects 15-21 (200 mg b.i.d [Group 3])*
Day 1	pre dose; 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16*, & 24 h post dose	pre AM dose; 0.5, 1, 2, 3, 4, 6. 8, 10, 12 (pre PM dose), & 24 h post AM dose
Day 3-6	predose	pre AM dose
Day 7	pre dose; 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16* & 24 h post dose	pre dose; 0.5, 1, 2, 3, 4, 6. 8, 10, 12, 16, & 24 h post dose
Day 9	X (48 hours post final dose)	
Day 10	X (72 hours post final dose)	

* as detailed in protocol amendment 1; also, measurements added at 48 hr & 72 hr post final dose for Groups 1 & 2

Urine sampling times: Urine was collected at the following times: pre-dose, 0-4, 4-8, 8-12, and 12-24 h post dose on Days 1 and 7.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, $t_{1/2}$) of SPM 927.

Analytical Methodology: Same as Study SP835

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOV A) was performed and the 90% confidence intervals were generated for the ratio of fed/fasted for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, $C_{max,}$ and $AUC_{0-\infty}$ were natural-log (In) transformed prior to analysis.

Results:

Study Population: 21 male Caucasian subjects were enrolled and they all completed the trial. The mean age of the subjects was 32 years (range, 19-39 years).

Pharmacokinetics: Mean PK profiles of SPM 927 for all the treatments are shown in Figures 1 and 2. Trough concentrations of SPM indicate that with a twice-daily dosing regimen with 200 mg LCM, steady state was reached after 72 hours.

Descriptive statistics for PK parameters of shown Table 1.

Figure 1. Mean Plasma Concentrations of SPM 927 After Oral Administration of SPM to Healthy Volunteers.

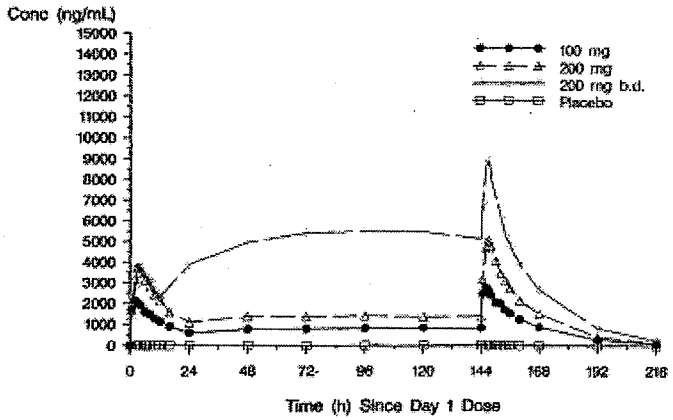

Figure 2. Mean Urinary Concentrations of SPM 927 After Oral Administration of SPM mg to Healthy Volunteers.

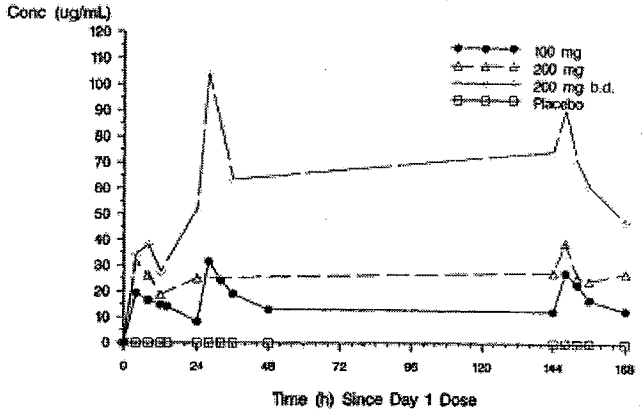

Table 1: Summary of PK Parameters

Dose	100 mg od		200 mg od		200 mg b.i.d.	
C_{max}	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Mean	2232.1	2955.3	3855.4	5167.6	4052.3	8902.6
SD	328.6	476.9	270.5	648.4	596.3	1426.7
Median	2151.8	2834.8	3961.5	5247.4	4205.9	8284.9
CV%	14.7	16.2	7.0	12.5	14.7	16.0
Minimum	1908.9	2426.1	3436.0	4022.9	3435.6	7571.7
Maximum	2701.1	3764.4	4144.9	5858.5	4857.4	11149.4
N	6	6	6	6	5	5
T_{max} (h)						
Mean	1.750	1.333	3.167	2.833	3.200	2.400
SD	0.880	0.753	1.472	0.753	0.837	0.548
Median	2.000	1.500	3.000	3.000	3.000	2.000
CV%	50.305	56.458	46.483	26.568	26.146	22.822
Minimum	0.500	0.500	2.000	2.000	2.000	2.000
Maximum	3.000	2.000	6.000	6.000	4.000	3.000
N	6	6	6	6	5	5
$AUC_{0\text{-}12}$						
Mean	18963.1	25244.1	33048.3	45466.7	34233.1	81369.3
SD	2169.2	3526.2	2528.7	5933.2	4439.7	11250.4
Median	19047.0	25465.4	33759.8	47388.8	34963.8	75023.4
CV%	11.4	14.0	7.7	13.0	13.0	13.8
Minimum	16476.7	21130.5	28768.2	34834.4	28767.5	72158.6
Maximum	21300.0	30833.0	35455.4	51569.0	40384.5	98587.2
N	6	6	6	6	5	5
$AUC_{0\text{-}72}$ (h·ng/mL)						
Mean	--	57220.7	--	98610.0	--	178352.1
SD	--	9583.5	--	23554.9	--	20453.9
Median	--	57129.7	--	100247.5	--	180537.4
CV%	--	16.7	--	23.9	--	11.5
Minimum	--	46363.7	--	61457.4	--	156874.8
Maximum	--	71399.0	--	123825.7	--	204049.5
N	--	6	--	6	--	5
$AUC_{0\text{-}\infty}$						
Mean	--	59129.0	--	101068.7	--	183309.2
SD	--	10343.8	--	24998.8	--	21433.9
Median	--	58884.9	--	102726.2	--	188436.4
CV%	--	17.5	--	24.7	--	11.7
Minimum	--	47224.5	--	61902.9	--	159509.5
Maximum	--	73624.6	--	127009.3	--	209133.8
N	--	6	--	6	--	5
λ_z Values (/h)						
Mean	--	0.048	--	0.054	--	0.050
SD	--	0.005	--	0.008	--	0.004
Median	--	0.049	--	0.051	--	0.050
CV%	--	10.6	--	14.7	--	8.9
Minimum	--	0.040	--	0.045	--	0.044
Maximum	--	0.055	--	0.068	--	0.056
N	--	6	--	6	--	5
$t_{1/2}$ (h)						
Mean	--	14.47	--	13.02	--	13.91
SD	--	1.67	--	1.80	--	1.23
Median	--	14.20	--	13.50	--	13.81
CV%	--	11.54	--	13.80	--	8.99
Minimum	--	12.70	--	10.26	--	12.23
Maximum	--	17.48	--	15.47	--	15.80
N	--	6	--	6	--	5

The $AUC_{0\text{-}\infty}$ was calculated using the concentrations from 0 h to 72 h.
-- = No measurement at this point

Comments: The PK parameters AUC(0-tz), AUC(0-∞), and Cmax increased proportionally with the administered daily doses of 100, 200, and 400mg. Tmax and t1/2 were unchanged at the different doses. Dose proportionality of AUC and Cmax was also shown by plotting mean Cmax, AUC(0-tz), and AUC(0-∞) against the daily dose and by the ratios of mean AUC(0-tz) and Cmax values between dose groups.

Steady state was reached after 72 hours of dosing with a twice-daily oral dosing regimen

PK conclusion: The analysis of $AUC_{(0\text{-}tz)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} of LCM showed dose-proportional increases for these parameters. The maximum plasma concentration was reached between 0.5 and 6 hours after dosing. The terminal half-life of LCM was approximately 13 to 14 hours.

4.2.2.2.2 Study SP588: Multiple dose tolerance study with ascending oral doses of SPM 927 (Harkoseride) in healthy male Caucasian volunteers

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Study Type: Multiple dose study.

Clinical Investigator: [redacted] b(4)

Objectives: To evaluate the safety, tolerability, PD effects, and pharmacokinetics of oral multiple doses of SPM 927.

Study Design: This was a randomized (within group), double-blind, placebo-controlled, sequential parallel-group study in subjects with single- and multiple-dose administration of LCM capsules filled with powder blend. Thirty-three subjects in total were enrolled in 2 sequential groups with ascending dose levels. The higher dose level in the second group was only administered after an evaluation of tolerability and safety data from the first group. Sixteen subjects were enrolled in the first group and randomized to 300 mg LCM as single dose on Day 1 and twice daily for 13.5 days on Days 3 to 16 (12 subjects) or matching placebo treatment (4 subjects). Seventeen subjects were enrolled in the second group and randomized to 500 mg LCM as single dose on Day 1 and twice daily for 13.5 days on Days 3 to 16 (12 subjects) or matching placebo treatment (5 subjects). The dose regimen in the second group could be altered during the trial for tolerability and safety reasons.

Blood sampling times: Serial blood samples (7 ml) were collected post dose on Days 1 16 and at several times on other days.

Urine sampling times: Urine was collected on Days 1, 3 and 16 at the following times: pre-dose(only on Day 1), 0-4, 4-8, 8-12, and 12-24 h post dose; over 24 hours on Days 2 and 17; and 0-12 hours after evening dose on day 15..

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