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2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Absorption:

Pharmacokinetics parameters of lacosamide following oral administration to mice.

Dose [mg/kg]	Duration	C_{max} [µg/mL]		T_{max} [h]		AUC_{last} [h·µg/mL]	
		Male	Female	Male	Female	Male	Female
20	Single dose	10.3	-	0.5[a]	-	32.6	-
	1 day	13.5	10.1	1	0.5[a]	33.4	28.3
	14 days	15.6	12.8	0.5[a]	0.5[a]	35.9	29.2
	6 months	12.6	11.8	0.5[a]	0.5[a]	36.3	27.8
	1 year	16.4	16.4	0.5[a]	0.5[a]	47.8	40.2
	2 years	12.6	10.5	0.5[a]	0.5[a]	28.9	33.5
30	1 day	16.0	18.8	1.0	0.5[a]	60.5	48.4
		17.7	16.9	0.5[a]	0.5[a]	47.9	58.8
	14 days	16.8	14.0	0.5[a]	0.5[a]	45.8	39.5
	3 months	20.0	20.4	0.5[a]	0.5[a]	51.5	46.2
60	1 day	32.6	16.6	1	0.5[a]	127	70.8
		26.9	24.7	0.5[a]	0.5[a]	95.1	96.5
	14 days	41.6	29.5	0.5[a]	0.5[a]	123	81.4
	3 months	29.0	27.6	0.5[a]	0.5[a]	97.0	131
	6 months	29.9	29.0	0.5[a]	1	103	86.3
	1 year	33.9	37.0	0.5[a]	0.5[a]	103	95.3
	2 years	29.8	30.4	0.5[a]	0.5[a]	99.0	92.9
90	1 day	38.3	39.9	0.5[a]	0.5[a]	140	151
	14 days	24.8	30.1	0.5[a]	0.5[a]	154	91.3
120	1 day	40.5	46.3	1	0.5[a]	189	205
	3 months	42.4	36.6	0.5[a]	0.5[a]	229	170
180	Single dose	61.5	-	0.5[a]	-	250	-
	1 day	46.7	38.9	0.5[a]	2	258	224
		56.1	81.5	1	1	269	362
	14 days	103	32.9	0.5[a]	0.5[a]	244	239
	3 months	53.8	45.9	0.5[a]	0.5[a]	315	240
	6 months	54.4	44.7	0.5[a]	0.5[a]	269	225
	1 year	78.8	44.7	0.5[a]	1	306	193
	2 years	78.5	62.5	0.5[a]	0.5[a]	230	233
270	1 day	140	76.0	0.5[a]	1	329	382
	14 days	53.6	40.7	1	2	458	283

Individual data or medians from 2 profiles are shown.
a - first sampling time
Data sources: Table 2.6.5.3B, — 18447/04; Table 2.6.5.3C, — 18772/05; Table 2.6.7.3; 4.2.3.2.1 — 13122/00, Appendix 9-3; 4.2.3.2.2, — 13123/00, Appendix 10-5, 4.2.3.4.1.1, — 13124/00, Appendix 11-5.

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Pharmacokinetics parameters of lacosamide following oral administration to rats.

Dose [mg/kg]	Duration	C_{max} [µg/mL]		T_{max} [h]		AUC_{last} [hr·µg/mL]	
		Male	Female	Male	Female	Male	Female
30	1 day	10.7	13.0	0.5[a]	1	62.4	78.3
		12.9	14.0	1	1	106	119
	3 months	12.0	14.4	1	1	61.3	80.8
		11.6	13.7	2	0.5[a]	121	134
	6 months	11.2	12.4	1	1	140	131
40	6 months	17.6	27.5	0.5[a]	0.5[a]	169	185
	1 year	20.8	22.2	0.5[a]	0.5[a]	177	190
	2 years	15.2	17.9	0.5[a]	0.5[a]	180	202
80	6 months	27.6	34.4	0.5[a]	1	299	429
	1 year	34.8	46.6	1	1	333	371
	2 years	27.1	29.3	0.5[a]	0.5[a]	373	342
90	1 day	23.6	25.3	1	2	262	311
	3 months	27.9	26.4	0.5[a]	1	275	310
	6 months	21.8	33.7	4	1	296	339
100	1 day	21.8	22.0	0.5[a]	1	147	152
	3 months	27.0	36.0	2	1	172	229
160	6 months	48.9	57.0	2	0.5[a]	514	659
	1 year	57.9	-	2	-	512	-
	2 years	49.5	-	1	-	605	-
180	1 day	32.7	30.7	1	0.5[a]	400	481
	3 months	38.2	33.9	2	1	539	501
	6 months	47.0	62.4	0.5[a]	1	488	570
	1 year	-	59.6	-	1	-	687
200	2 years	-	51.6	-	0.5[a]	-	737
300	1 day	34.2	40.3	1	2	218	216
	3 months	57.6	57.1	1	1	340	408

Values are medians or means (n = 2 to 3 profiles) or pharmacokinetic parameters were calculated with mean plasma concentrations.
a - first sampling time
Data sources: 4.2.3.2.5, 148-235, Pharmacokinetic evaluation report; 4.2.3.2.6. — 3227/00, Appendix 10-5; 4.23.4.1.2 — 3295/00, Appendix 11-5.

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Pharmacokinetics parameters of lacosamide following oral administration to adult dogs.

Dose [mg/kg]	Duration	C_{max} [µg/mL]		T_{max} [h]		AUC_{last} [h·µg/mL]	
		Male	Female	Male	Female	Male	Female
5	1 day	7.35	6.11	1	1.5	18.4	21.0
	3 months	7.13	6.60	1	1	22.8	23.0
	9 months	5.79	5.40	1.5	1.3	19.8	21.0
	1 year	7.07	7.36	0.5	1.3	31.4	24.5
6	1 day	6.75	7.60	1 (0.5-1)	0.5 (0.25[a]-1)	19.7	22.9
		9.11	8.60	0.8 (0.5-1)	0.8 (0.5-1)	20.9	21.7
	3 weeks	7.36	7.37	0.8 (0.5-1)	1 (0.5-1)	21.0	23.2
	3 months	9.47	6.24	0.5 (0.25[a]-1)	1 (0.5-2)	27.1	19.4
10	1 day	12.1	9.97	1.3	1.3	43.8	35.5
	3 months	13.4	14.6	0.5	1.5	43.7	58.1
	9 months	14.5	12.7	0.5	1	74.1	49.8
	1 year	15.5	13.2	0.8	1.3	71.0	54.6
12	1 day	12.7	10.8	0.8 (0.5-2)	1.5 (0.5-2)	46.1	44.5
		16.7	15.3	0.5 (0.25[a]-1)	0.6 (0.25[a]-1)	31.6	29.8
	3 weeks	13.4	14.9	1 (0.5-2)	1 (0.5-1)	48.4	51.8
	3 months	17.0	15.6	0.5 (0.5-0.5)	1.5 (0.5-2)	49.0	45.5
12 (bid)	1 day	13.9±1.6	-	0.5[a] (0.5[a]-1)	-	42.1±6.1	-
	8 days	13.6±1.6	-	1 (0.5[a]-2)	-	43.5±10.1	-
16 (bid)	1 day	18.1±2.7	-	1 (1-2)	-	69.8±8.0	-
	8 days	16.7±1.8	-	1 (1-1)	-	61.8±14.3	-
24	1 day	23.5	23.5	0.8 (0.25[a]-2)	1 (0.5-2)	83.1	79.5
		27.1	27.4	1 (0.5-2)	1 (0.25[a]-1)	65.2	59.4
	3 weeks	20.7	28.6	3 (1-4)	1 (0.5-2)	82.7	107
	3 months	32.8	27.6	0.5 (0.25[a]-1)	0.8 (0.25[a]-1)	102	85.2
25	1 day	23.1	17.1	1	1.5	95.6	68.6
	3 months	26.7	25.3	1.5	2	124	129
	9 months	29.9	27.4	1	1.5	166	133
	1 year	23.9	18.9	1.3	1	142	124

Values are means (± SD) (n=2, 4 or 5) except for T_{max} (median (range)). AUC_{last} was determined over one dose interval.
a - first sampling time
bid = twice daily (12 hours apart)
Data sources: Table 2.6.5.3[illegible] —— 5654.02; 4.2.3.2.10, 98825 [illegible]acokinetic evaluation report; 4.2.3.2.11, 98865, Toxicokinetic evaluation report; 4.2.3.2.12, —— 196.00, Appendix 10-5.

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Comparative pharmacokinetic data and systemic exposure to lacosamide following intravenous administration of lacosamide to dogs and human volunteers.

Species Route	Sex	Dose [mg/kg/day]	Parameter [unit] C_{max} [µg/mL]	$T_{1/2}$ [h]	AUC_{0-inf} [h·µg/mL]
Dog intravenous (bolus)	Male	4	6.7 ± 1.0	1.9 ± 0.3	25.3 ± 7
		8 (NOEL)	13.0 ± 0.5	1.7 ± 0.2	45.9 ± 4
		16	26.1 ± 1.4	2.1 ± 0.1	106 ± 4
	Female	4	6.4 ± 0.6	1.6 ± 0.3	22.3 ± 5
		8 (NOEL)	15.3 ± 1.8	1.7 ± 0.2	53.7 ± 7
		16	25.4 ± 1.2	1.7 ± 0.1	93.9 ± 7
Man intravenous (10 minutes)	Male	0.7 [a]	1.4 ± 0.6	13.5 ± 1.5	20.3 ± 2.5
		1.4 [a]	3.8 ± 1.3	12.2 ± 2.6	44.3 ± 6.6
		2.1 [a]	5.8 ± 1.9	12.3 ± 2.3	62.3 ± 13
		4.3 [a]	11.8 ± 2.5	12.3 ± 0.8	111 ± 12

Data presented are after repeated intravenous bolus injection at the end of a 14-day dog study (mean ± SD, n=4 per sex) or after single 10-minute intravenous infusion to healthy young male volunteers (mean ± SD, n= 5 to 6).
a - In man a body weight of 70 kg was assumed (50, 100, 150, 300 mg per subject).
Data sources: 4.2.3.2.14, 98793, Pharmacokinetic evaluation report; 5.3.3.1.5, SP834, Table 14.2.1.

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Comparative pharmacokinetic data following repeated oral administration of lacosamide to mice, rats, dogs and human volunteers.

Species Route	Sex	Dose [mg/kg/day]	Parameter of lacosamide [unit] C_{max} [µg/mL]	T_{max} [h]	AUC_{last} [hµg/mL]
Mouse	Male	30	20.0	0.5	51.5
Oral		60 (NOAEL)	29.0	0.5	97.0
(solution)		120	42.4	0.5	229
		180	53.8	0.5	315
	Female	30	20.4	0.5	46.2
		60 (NOAEL)	27.6	0.5	131
		120	36.6	0.5	170
		180	45.9	0.5	240
Rat	Male	30	11.2	1	140
Oral		90 (NOAEL)	21.8	4	296
(solution)		180	47.0	0.5	488
	Female	30	12.4	1	131
		90 (NOAEL)	33.7	1	339
		180	62.4	1	570
Dog	Male	5	7.1	0.5	31.4
Oral		10 (NOAEL)	15.5	0.8	71.0
(capsule)		25	23.9	1.3	142
	Female	5	7.4	1.3	24.5
		10 (NOAEL)	13.2	1.3	54.6
		25	18.9	1.0	124
Man	Male	8.6 Day 15 (night)	12.6 ± 2.2	3 (1 - 6)	119 ± 18.3
Oral (capsule)		Day 16 (day)	14.5 ± 1.7	1 (1 - 2)	126 ± 17.4

Data presented are after repeated oral administration at the end of a 3-month mouse (individual data), 6-month rat (medians, n=3), 12-month dog (medians, n=2) and 16-day human trial SP588 (means ± SD, n=12, T_{max} median (range)). In man a body weight of 70 kg was assumed (2 x 300 mg per subject/day).
$AUC_{0-8 h}$ in the mouse, rat and dog, and $AUC_{0-12 h}$ in man are given.
Data sources: 4.2.3.2.2, — 13123/00, Appendix 10-5, 4.2.3.2.6, — 3227/00, Appendix 10-5; 4.2.3.2.12, — 13196/00, Appendix 10-5; 5.3.3.1.4, SP588, Section 9.4.

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Metabolism:

Metabolism: Interspecies comparison of maximum observed concentration of plasma metabolites.

Metabolite	RT [min]	ng equivalents/mL							
		Male mouse oral	Female mouse oral	Male rat oral	Female rat oral	Male dog oral	Female dog oral	Male dog intravenous	Female dog intravenous
MP1, RP1, DP1	2.85	603	937	437	380	-	<LOQ	76.3	-
RP2	3.13	-	-	-	<LOQ	-	-	-	-
MP2	4.10	137	-	-	-	-	-	-	-
MP3	4.67	44	-	-	-	-	-	-	-
MP4, RP3, DP2	6.64	240	311	300	298	-	-	48.0	77.6
MP5, RP4, DP3	7.52	-	244	<LOQ	-	218	208	-	-
DP4	17.7	-	-	-	-	492	404	782	560
DP5	18.2	-	-	-	-	<LOQ	-	45.6	-
DP6	20.8	-	-	-	-	138	158	146	155
DP7	22.8	-	-	-	-	261	242	342	322
DP8	23.6	-	-	-	-	60.6	-	99.6	<LOQ
DP9	25.6	-	-	-	-	-	-	-	<LOQ
MP6, RP5, DP10	26.1	<LOQ	410	774	433	556	674	559	673
MP7, RP6, DP11	27.3	1011	1278	<LOQ	-	<LOQ	<LOQ	<LOQ	<LOQ
MP8, DP12	29.2	220	292	-	-	-	-	-	1462

Major metabolites in plasma following single oral administration of [14C]-lacosamide to mice, rats and dogs.

Region or Compound	Retention time [minutes]	Maximum % of radioactivity in chromatogram					
		Mouse		Rat		Dog	
		Male	Female	Male	Female	Male	Female
Polar peak	3	13.7	27.0	2.45	2.40	-	-
Medium polar fraction	18 - 24	-	-	-	-	13.9	15.2
SPM 12817 (p-M2)	26	BLQ	2.27	4.34	2.73	5.40	7.73
SPM 6912 (M5)	27.5	6.86	8.98	BLQ	-	BLQ	BLQ
Unknown	29	4.98	8.41	-	-	-	-
SPM 12809 (M1)	30	17.2	22.0	15.4	17.1	33.4	36.2
Lacosamide	37	70.0	75.7	62.2	78.1	88.6	88.3

Data presented are after single oral administration [^{14}C]-lacosamide at 20 (mice), 40 (rats) and 10 mg/kg (dogs).
Plasma samples were obtained at the following times post dose: 1 and 6 hours (mouse), 4 and 24 hours (rat), dog: 10 minutes, 0.5, 1, 2, 4, 8, 12, 24 and 48 (dog).
BLQ = below the limit of quantification (1% of radioactivity), - = not detected

Major metabolites in urine following single oral administration of [^{14}C]-lacosamide to mice, rats and dogs.

Compound	Retention time [minutes]	% of administered dose					
		Mouse		Rat		Dog	
		Male	Female	Male	Female	Male	Female
Unknown	3	3.23	2.88	-	-	0.449	BLQ
Unknown	6	3.20	2.76	2.94 [b]	3.10	2.84	2.40
Unknown [a]	8	0.835	1.27	3.55 [b]	3.02	1.15	1.75
M4 (GlcUA of M2)	17	-	-	BLQ	BLQ	10.5	8.26
SPM 12814 (p-M3)	21	-	-	0.264	BLQ	3.41	4.57
Sulfate of M2	22.5	-	-	-	-	5.97	6.44
SPM 12817 (p-M2)	26	-	-	12.3	9.72	5.36	7.10
SPM 6912 (M5)	27.5	3.15	2.81	-	-	BLQ	-
M6	29	1.91	1.87	0.792	0.549	BLQ	-
SPM 12809 (M1)	30	17.1	19.5	30.5	32.6	31.8	32.5
Lacosamide	37	16.9	18.5	12.2	25.6	8.0	6.13
Total		**54.5**	**51.7**	**72.3**	**78.5**	**79.4**	**77.9**

Data presented are after single oral administration [^{14}C]-lacosamide at 20 (mice), 40 (rats) and 10 mg/kg (dogs).
Pooled urine samples (0-24 hours) were investigated by radioHPLC-MS/MS
a - Investigations with [^{14}C] lacosamide labeled either at the carboxylic or at the benzylic carbon atom suggest the formation of a desbenzylamine derivative (4.2.2.4.6, 847).
b - When employing the HPLC method which was used for human urine from trial SP619, the 6- and 8-minute peaks co-eluted as one peak at a retention time of 1.6 minutes (4.2.2.1, 1000)
BLQ = below the limit of quantification (0.15 - 0.63% of the dose). - = not detected

Excretion:

Mice: Excretion of radioactivity following single administration of [^{14}C]-lacosamide.

Species	Sex	Dose [mg/kg]	Route of administration	Percentage of administered dose			
				Urine	Feces	Carcass	Total
Mouse	Male	20	oral (single)	83.1 ± 7.1	4.5 ± 2.0	1.8 ± 0.2	90.1 ± 4.8
	Female	20	oral (single)	80.9 ± 2.5	5.3 ± 2.3	1.7 ± 0.2	88.7 ± 3.0

Excretion was determined over 168 hours. Values are means ± SD (n = 3). Urine includes cage wash (24.5% ± 11.3% in males and 23.9% ± 13.0% in females). Total includes radioactivity in cage debris.
Data source: Table 2.6.5.13A, 699/46

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Rat: Excretion of radioactivity following single administration of [^{14}C]-lacosamide.

Species	Sex	Dose [mg/kg]	Route of administration	Percentage of administered dose			
				Urine	Feces	Carcass	Total
Rat	Male	10	oral (single)	81.8 ± 2.9	16.3 ± 3.1	1.6 ± 0.2	99.7 ± 1.1
	Male	10	iv (single)	78.1 ± 7.2	17.6 ± 6.7	1.8 ± 0.5	98.0 ± 5.0
Rat	Male	10	oral (single)	81.1 ± 1.5	8.0 ± 0.5	3.9 ± 0.3	92.9 ± 1.2
	Male	10	oral (repeat)	79.8 ± 1.0	8.0 ± 4.7	3.7 ± 0.9	91.5 ± 0.7
	Female	10	oral (single)	82.8 ± 2.8	4.5 ± 2.0	3.3 ± 0.5	90.7 ± 1.2
Rat	Male	40	oral (single)	83.0 ± 1.5	8.0 ± 0.9	3.5 ± 0.6	94.5 ± 2.0
	Female	40	oral (single)	86.0 ± 2.6	4.1 ± 1.2	3.9 ± 0.6	94.0 ± 0.9

Excretion was determined over 72 or 168 hours. Values are means ± SD (n=3). Urine includes cage wash (<15%). Total includes radioactivity in cage debris (<0.1%) and in expired air (<0.5%).
Data sources: Table 2.6.5.13B, F212; Table 2.6.5.13C, 699/47; Table 2.6.5.13D, 0699/023

Dogs: Excretion of radioactivity following single administration of [^{14}C]-lacosamide.

Species	Sex	Dose [mg/kg]	Route of administration	Percentage of administered dose		
				Urine	Feces	Total
Dog	Male	10	oral (single)	85.4 ± 7.4	7.2 ± 6.7	92.6 ± 3.5
	Male	10	iv (single)	75.9 ± 11.6	7.1 ± 6.6	83.0 ± 11.9
Dog	Male	10	oral (single)	84.7	7.2	92.1 [a]
	Female	10	oral (single)	84.2	7.5	91.8 [a]
	Male	10	iv (single)	88.1	6.6	95.0 [a]
	Female	10	iv (single)	88.0	6.6	94.8 [a]

Excretion was determined over 72 or 168 hours. Values are means ± SD (n = 3) or medians (n = 2). Urine includes cage wash (< 11%).
a - Total includes radioactivity in cage debris (<0.3%)
Data sources: Table 2.6.5.13E, F232; Table 2.6.5.13F, 699/48

Human: Excretion of radioactivity following single administration of [^{14}C]-lacosamide.

Species	Sex	Dose [mg]	Route of administration	Percentage of administered dose		
				Urine	Feces	Total
Man	Male	100	oral (single)	94.19 ± 3.09	0.38 ± 0.17	94.57 ± 3.12
	Male	100	iv (1-hour, single)	96.82 ± 2.62	0.30 ± 0.07	97.13 ± 2.65

Excretion was determined over 168 hours in healthy male human subjects following single oral administration or after 1-hour intravenous infusion of 100 mg [^{14}C]-lacosamide. Values are means ± SD (n = 5 per group).
Data source: 5.3.1.1.1, SP619, Table 13.9, Table 13.10

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

In support of the chronic indication, the systemic toxicity of lacosamide was studied in mice, rats, dogs and rabbits. The key repeat-dose toxicology studies to support the chronic indication were conducted in mice up to 13 weeks, in rats up to 6 months and up to 12 months in dogs.

In a 13-week repeat dose mouse study, CD-1 mice were administered lacosamide by oral gavage at doses of 30, 60, 120 and 180 mg/kg/day. Dose levels were based on the findings of the 2-week dose-range finding study (— 13122/00). Clinical signs of toxicity included ataxia, abdominal position and reduced motility at 120 and 180 mg/kg/day. Ataxia was observed in all animals on the first day of dosing and was observed on most days of the study. Reduced motility was not observed until day 16 of the study and was observed in all animals until termination of the study. Two deaths occurred in the high dose group (180 mg/kg). There were no microscopic findings in this study. The NOAEL was 60 mg/kg/day based on clinical signs not considered to be significant safety issues. This NOAEL was associated with a mean $AUC_{(0-24)}$ of 97.0 μg.h/mL in males and C_{max} of 29.04 μg/mL (males) and 27.62 μg/mL (females). b(4)

In the 13-week repeat dose rat study, Sprague-Dawley rat were administered lacosamide by oral gavage at doses of 30, 100 and 300 mg/kg/day. Dose levels were based on the findings of the 1-month dose-range finding study (— 1108-005). In the dose-range finding study, female rats were orally administered lacosamide at dosages of 0, 100, 200 and 300 mg/kg to determine the MTD. At the highest dose (300 mg/kg/day), two treatment-related deaths occurred in week 1. At 200 mg/kg/day and higher, clinical signs of toxicity included muscle flaccidity, decreased motor activity, impaired righting reflex, splayed limbs, ataxia and head bobbing. In addition to these clinical signs, loss of righting reflex, bradypnea and excessive salivation were observed at 300 mg/kg/day. Based on these clinical signs, the NOAEL was 100 mg/kg and the MTD was established at ≤ 200 mg/kg/day. In the 13-week study, treatment-related clinical signs included ataxia, hypoactivity, prostration and convulsions (female only). Five deaths, which were attributed to lacosamide, occurred in the female high dose group. Treatment-related increases in mean liver-to-body weight were noted in both males and females at all dose levels. The increase in liver weight in the high dose female group was attributed to the observed increase in alanine aminotransferase and alkaline phosphatase. Changes in urine chemistry indicate that lacosamide has a diuretic-like effect. Significant increases in urine volume were observed in both male and females starting at the lowest dose (30 mg/kg/day). Based on clinical signs, not considered to be safety issues, 100 mg/kg/day (mean C_{max} of 906 ng/mL and mean AUC of 14,252 ng.h/mL) was established as the NOAEL in this study. b(4)

A 6-month oral toxicity study was conducted in rats that dosed the animals once daily with 0 (vehicle), 30, 90 and 180 mg/kg/day. The top dose was selected based on a dose-range finding study (Study Report № 1108-005) that was conducted in rats that observed minimal toxicity at 100 mg/kg/day. In the 6-month study, clinical signs of toxicity included excessive salivation, reduced motility, increased muscle tone, abdominal or lateral position and apathy in the high-dose group (180 mg/kg/day). These clinical signs

had a rapid onset, starting 15 to 20 minutes after dosing, and lasting for a few hours (reduced motility) or up to 24 hours (salivation). The observed reduced motility and apathy peaked within the range of T_{max} for lacosamide. Three deaths occurred in the study; one female in the control group, one female in the low dose group and one male in the high dose group. The Sponsor concluded that the death of the male was treatment-related. However, no macroscopic changes were identified. A marginal but dose-related (90 to 180 mg/kg/day) reduction in body weight was observed in the male rats. At the end of the dosing period (day 182), relative to control, a 7% reduction in body weight was noted in the males in the high dose group. Serum cholesterol levels were significantly increased by 41% and 25% in females at 180 mg/kg/day in weeks 13 and 26, respectively. Although not statistically significant, compared to the control, serum cholesterol levels were increased by 29% and 20% at weeks 13 and 26, respectively, in males at 180 mg/kg/day. Increased ALT levels were noted in the rats at 180 mg/kg/day. At week 13, ALT levels in females were significantly increased by 43%. ALT levels were increased by 30% (not statistically significant) at week 13 in females in the high dose group. Also at 180 mg/kg/day, the relative liver weight and liver-to-brain weight was significantly increased by 13.3% and 14.8%, respectively, compared to the control. No macroscopic or histopathological changes in the liver of females in the high dose group were observed. The increased ALT activities and increased liver weights were reversible; within the 4-week recovery period, the ALT levels and liver weights were within normal range. Urinalysis results suggest that lacosamide can produce a diuretic-like effect. At 180 mg/kg/day, the urine volume was increased by 12% and 84% in males and females, respectively. Also the high dosed female, drinking water consumption was transiently increased up to 21% compared controls in week 6. Specific gravity was minimally, but statistically significantly, decreased in females at 90 and 180 mg/kg/day. The NOAEL was 90 mg/kg/day based on clinical signs not considered to be significant safety issues. This NOAEL was associated with a mean $AUC_{(0-24)}$ of 325.8 h.μg/mL and C_{max} of 27.45 μg/mL.

A 12-month oral toxicity study was conducted in dogs that dosed animals once daily with 0, 5, 10, 20 (first 5 weeks) and 25 mg/kg. The high dose was adjusted from 20 to 25 mg/kg/day in week 6 because 20 mg/kg/day only produced mild systemic toxicity. No deaths occurred during the study. Consistent with the observed clinical signs in rodents, lacosamide produced evidence of CNS and gastrointestinal toxicity in dogs. At 20 mg/kg/day, vomiting, tonic-clonic convulsions, sedation, ataxia, abdominal and/or lateral position, were observed among a few dogs on some isolated days. At 25 mg/kg/day, these clinical signs were observed in more dogs and were more pronounced and occurred more frequently. Also new clinical signs, i.e. reduced motility, tremor, salivation, increased defecation and vocalization, emerged. Onset of the clinical signs was generally at C_{max} between 5 and 60 minutes after dosing and lasted for up to 2 hours; increased salivation was noted for 24 hours. EKG data were obtained on test days 1 and 3, and at the end of weeks 13, 26, 39 and 52. Blood pressure data was obtained before and 2.5 hours after dosing at the end of weeks 13, 26, 39 and 52. Cardiac effects were minimal following oral administration of lacosamide. In females, a dose-dependent decrease in peripheral arterial systolic blood pressure was noted on test day 1. Statistically significant decrease in peripheral arterial blood pressure was observed at 10 mg/kg/day

(30% decrease) and 20 mg/kg/day (35% decrease). During week 13, a 37% decrease in peripheral arterial blood pressure was observed compared to control. No further lacosamide-related effects was observed after week 13. In males, there was no lacosamide-related effect on blood pressure up to 25 mg/kg. Single statistically significant changes appeared to be inconsistent in direction (increase / decrease), not dose-related and/or were observed prior to dosing. Lacosamide did not induce significant ECG changes. No treatment-related changes were observed in QRS interval, PQ interval, P-segment and QT electrocardiographic complexes in either male or females. A statistically significant increase of the QTc (as calculated by Fridericia) value for high dose females was caused by relatively low QTc values of the controls and considered to be within the normal range. The NOAEL was 10 mg/kg/day based on the lack of toxicological findings and on the increased heart rate not being statistically significant and is monitorable. This corresponds to AUC values of 71.0 and 54.6 h.µg/mL in males and females respectively, after repeated daily dosing for 12 months. C_{max} values at this dose were 15.52 and 13.15 µg/mL in males and females, respectively.

Genetic toxicology:

The Sponsor conducted five genetic toxicology studies to evaluate the genotoxicity and/or mutagenicity of lacosamide. Three of the five studies were in vitro studies and the remaining 2 studies were in vivo Dr. Edward Fisher reviewed these studies, specific details can be found in the NDA (NDA № 22-253) review prepared by Dr. Fisher.

Carcinogenicity:

To evaluate the carcinogenic potential of lacosamide, the Sponsor conducted a 2-year carcinogenicity bioassays were in mice and rats. Drs. Edward Fisher and Terry Peters reviewed these studies. Specific details of these studies can be found in NDA 22-253 review from Drs. Fisher and Peters.

Reproductive toxicology:

The Sponsor conducted a standard battery of reproductive toxicology studies. Dr. Edward Fisher reviewed these studies. Specific details of these studies can be found in NDA 22-253 review from Dr. Fishers

2.6.6.2 Single-dose toxicity
Single-dose toxicology studies were conducted in mice and rats.

Study title: Acute Toxicity Study of SPM 927 by Oral Administration to CD-1 Mice.

Key study findings: A single dose of SPM 927 (31.6, 100, 316, and 464 mg/kg) was administered via gavage to mice. The mice were observed for 14 days following dosing. The following key findings were obtained:

b(4)

1. All animals in the high-dose group (464 mg/kg) died within 20 minutes to 2 hours after oral administration of lacosamide.
2. Reduced motility, mortality, ataxia, tremor, mydriasis, dysponea, increased muscle tone and abdominal position were the primary treatment-related clinical signs.
3. No treatment-related macroscopic changes were noted.
4. No treatment-related histological changes were observed in the liver or kidney.
5. Based on clinical signs, NOEL is 31.6 mg/kg.

Study №: Report No. — 3121/00 b(4)

Volume #, and page #: 4.23.1.1
Conducting laboratory and location: —

b(4)

Date of study initiation: April 18, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № KK 02457, 99.67%

Methods

Doses: 31.6, 100, 316, and 464 mg/kg b(4)
Species/strain: Mice/ — CD®
Number/sex/group or time point (main study): 3/sex/group
Route, formulation, volume, and infusion rate: Oral gavage, Solution, 20 mL/kg
Satellite groups used for toxicokinetics or recovery: None
Age: Males: 24 days; Females: 25 days
Weight: Males: 25-26 g; females: 20–25 g
Sampling times: N/A
Unique study design or methodology (if any): None

Observations and times:

Mortality: Mortality was examined once daily.
Clinical signs: Clinical signs were observed before and immediately, 5, 15, 30, and 60 minutes and 3, 6, and 24 hours after dosing. All surviving animals were observed for 14 days. During this 2-week period, the animals were observed once daily for changes in skin and fur, eyes and mucus membranes, respiratory and circulatory function, autonomic and central nervous system and somatomotor activity and behavioral pattern.
Body weights: Body weight was recorded pre-dosing, and than weekly until end of study.
Food consumption: Not monitored
Ophthalmoscopy: Not performed
EKG: Not performed
Hematology: Not performed
Clinical chemistry: Not performed

Urinalysis: Not performed
Gross pathology: Surviving animals were euthanized under ether anesthesia. Macroscopic evaluation was performed.
Organ weights: Relative organ weight of liver and kidney was calculated.
Histopathology: Liver and kidney were fixed in 7% buffered formalin and stained with haematoxylin-eosin stain prior to being examined microscopically.

Results

Mortality: Treatment-related deaths were observed. All subjects in the high-dose group (464 mg/kg) died within 20 minutes and 2 hours after dosing. The Sponsor reported that prior to their death; the animals were comatose and displayed an abdominal position (not described). LD_{50} for lacosamide at 24 hours and 14 days posting dosing was 383 mg/kg for both males and females.

Clinical signs: Treatment-related clinical signs were dose-dependent. No treatment-related clinical signs were observed in the low-dose group (31.6 mg/kg). As indicated in the table 1 below, reduced motility, ataxia, tremor, tonic convulsions, abdominal position, mydriasis, dysponea, and increased muscle tone were the primary treatment-related clinical signs. These primary treatment-related clinical signs had a rapid onset of action; occurring within 5 to 15 minutes after dosing. These clinical signs were observed for up to 6 hours.

Table 1

	Dose (mg/kg) (n = 3/sex/group)							
	31.6		100		316		464	
	M	F	M	F	M	F	M	F
Symptom								
Reduced Motility	0	0	3	3	3	3	0	0
Ataxia	0	0	3	3	3	3	0	0
Tremor	0	0	3	3	3	3	0	0
Tonic convulsion	0	0	0	0	3	3	3	3
Abdominal Position	0	0	0	0	3	3	3	3
Mydriasis	0	0	3	3	3	3	3	3
Dysponea	0	0	3	3	3	3	3	3
Increased Muscle Tone	0	0	3	3	3	3	3	3
Mortality	0	0	0	0	0	0	3	3

Body weights: No treatment-related effects on body weight were noted.

Gross pathology: At necropsy, all animals were observed for identifying macroscopic lesions. No treatment-related macroscopic changes were identified.

Organ weights: No treatment-related effects on relative liver and kidney weight were observed in any groups.

b(4)

Histopathology: Histological examination of the liver and kidney did not reveal any treatment-related changes

Study title: Acute Toxicity Study of SPM 927 by Single Oral Administration to CD Rats.

Key study findings: A single dose of lacosamide (31.6, 100, 316, and 464 mg/kg) was administered via gavage to rats. The rats were observed for 14 days following dosing. The following key findings were obtained:

1. All animals in the high-dose group (464 mg/kg) died within 3 hours after oral administration of lacosamide.
2. Reduced motility, mortality, ataxia, dyspnea, reduced muscle tone and lateral position were the primary treatment-related clinical signs.
3. No treatment-related macroscopic changes were noted.
4. Based on clinical signs, NOEL is 31.6 mg/kg.

b(4)

Study №: Report No. — 17964/04

Volume #, and page #: 4.2.3.1.3
Conducting laboratory and location: / / / b(4)

Date of study initiation: June 18, 2004
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № WE 11837 (537.1008, —, 99.6%

b(4)

Methods

Doses: 31.6, 100, 316, and 464 mg/kg
Species/strain: Rat/CD®
Number/sex/group or time point (main study): 3/sex/group
Route, formulation, volume, and infusion rate: Oral gavage, Solution, 20 mL/kg
Satellite groups used for toxicokinetics or recovery: None
Age: Males: 48 days; Females: 55 days
Weight: Males: 207-230 g; Females: 177–202 g
Sampling times: N/A
Unique study design or methodology (if any): None

Observations and times:
Mortality: Mortality was examined once daily.
Clinical signs: Clinical signs were observed before and immediately, 5, 15, 30, and 60 minutes and 3, 6, and 24 hours after dosing. All surviving animals were observed for 14

days. During this 2-week period, the animals were observed once daily for changes in skin and fur, eyes and mucus membranes, respiratory and circulatory function, autonomic and central nervous system and somatomotor activity and behavioral pattern.
Body weights: Body weight was recorded pre-dosing, and then weekly until end of study.
Food consumption: Not monitored
Ophthalmoscopy: Not performed
EKG: Not performed
Hematology: Not performed
Clinical chemistry: Not performed
Urinalysis: Not performed
Gross pathology: Surviving animals were euthanized under ether anesthesia. Macroscopic evaluation was performed.
Organ weights: Not performed
Histopathology: Not performed

Results

Mortality: No treatment-related deaths were observed in the 31.6 and 100 mg/kg groups. Treatment-related deaths were observed in the 316 and 464 mg/kg groups. One male and one female died in the 316 mg/kg group. All subjects in the high-dose group (464 mg/kg) died within 3 hours after dosing. The Sponsor reported that prior to their death; the animals were comatose and displayed an abdominal position (not described). LD_{50} for lacosamide at 24 hours and 14 days posting dosing was 383 mg/kg for both males and females.

Clinical signs: Treatment-related clinical signs were dose-dependent. No treatment-related clinical signs were observed in the low-dose group (31.6 mg/kg). As indicated in the table 2 below, reduced motility, ataxia, reduced muscle tone, clonic convulsions, lateral position, and dyspnea were the primary treatment-related clinical signs. These primary treatment-related clinical signs had a rapid onset of action; occurring within 5 to 15 minutes after dosing. These clinical signs were observed for up to 6 hours.

The Sponsor noted that reduced motility, ataxia, and dyspnea as slight to moderate. Reduced muscle tone ranged form slight to severe.

Body weights: No treatment-related effects on body weight were noted.

Gross pathology: At necropsy, all animals were observed for identifying macroscopic lesions. No treatment-related macroscopic changes were identified.

Table 2.

	Dose (mg/kg) (n = 3/sex/group)							
	31.6		100		316		464	
	M	F	M	F	M	F	M	F

Symptom								
Reduced Motility	0	0	3	3	2	3	1	2
Ataxia	0	0	3	3	2	3	1	2
Clonic convulsion	0	0	0	0	3	3	3	3
Lateral Position	0	0	1	0	3	3	3	3
Dyspnea	0	0	3	3	3	3	3	3
Reduced Muscle Tone	0	0	3	3	3	3	3	3
Mortality	0	0	0	0	1	1	3	3

Study title: Acute Toxicity Study of SPM 927 by Single Intravenous Administration to CD-1 Mice.

Key study findings: A single dose of lacosamide (10, 31.6, 100, and 316 mg/kg) was administered intravenous to mice. The mice were observed for 14 days following dosing. The following key findings were obtained:

1. All animals in the high-dose group (316 mg/kg) died within 15 hours after oral administration of lacosamide.
2. Reduced motility, death, ataxia, dyspnea, reduced muscle tone, tremor, clonic convulsions, abdominal position and lateral position were the primary treatment-related clinical signs.
3. No treatment-related macroscopic changes were noted.
4. Based on clinical signs, NOEL is 10 mg/kg.

Study №: Report No. — 17963/04 b(4)

Volume #, and page #: 4.23.1.2
Conducting laboratory and location: / / / / b(4)

Date of study initiation: June 18, 2004
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № WE 11837 (537.1008, — , 99.6%

Methods b(4)

Doses: 10, 31.6, 100, and 316 mg/kg
Species/strain: CD-1 Mice Rat — .CD1®
Number/sex/group or time point (main study): 3/sex/group
Route, formulation, volume, and infusion rate: Intravenous, Solution, 20 mL/kg, 15 sec infusion rat
Satellite groups used for toxicokinetics or recovery: None
Age: Males: 32 days; Females: 33 days
Weight: Males: 20-23 g; Females: 17–20 g
Sampling times: N/A
Unique study design or methodology (if any): None

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Observations and times:
Mortality: Mortality was examined once daily.
Clinical signs: Clinical signs were observed before and immediately, 5, 15, 30, and 60 minutes and 3, 6, and 24 hours after dosing. All surviving animals were observed for 14 days. During this 2-week period, the animals were observed once daily for changes in skin and fur, eyes and mucus membranes, respiratory and circulatory function, autonomic and central nervous system and somatomotor activity and behavioral pattern.
Body weights: Body weight was recorded pre-dosing, and then weekly until end of study.
Food consumption: Not monitored
Ophthalmoscopy: Not performed
EKG: Not performed
Hematology: Not performed
Clinical chemistry: Not performed
Urinalysis: Not performed
Gross pathology: Surviving animals were euthanized under ether anesthesia. Macroscopic evaluation was performed.
Organ weights: Not performed
Histopathology: Not performed

Results

Mortality: Treatment-related deaths were observed. All subjects in the high-dose group (316 mg/kg) died within 15 minutes after dosing. LD_{50} for lacosamide at 24 hours and 14 days posting dosing was 178 mg/kg for both males and females.

Clinical signs: Treatment-related clinical signs were dose-dependent. No treatment-related clinical signs were observed in the low-dose group (10 mg/kg). As indicated in the table 3 below, reduced motility, ataxia, reduced muscle tone, clonic convulsions, lateral position, abdominal position and dyspnea were the primary treatment-related clinical signs. These primary treatment-related clinical signs had a rapid onset of action; occurring within 0 to 5 minutes after dosing. These clinical signs were observed for up to 6 hours.

Body weights: No treatment-related effects on body weight were noted.

Gross pathology: At necropsy, all animals were observed for identifying macroscopic lesions. No treatment-related macroscopic changes were identified.

Table 3.

	Dose (mg/kg) (n = 3/sex/group)							
	10		31.6		100		316	
	M	F	M	F	M	F	M	F
Symptom								
Reduced Motility	0	0	3	3	3	3	0	0

Ataxia	0	0	3	3	3	3	0	0
Tremor	0	0	0	0	3	3	0	0
Clonic convulsion	0	0	0	0	3	3	3	3
Lateral Position	0	0	0	0	0	0	3	3
Abdominal Position	0	0	0	0	3	3	0	0
Dyspnea	0	0	3	3	3	3	3	3
Reduced Muscle Tone	0	0	0	0	3	3	0	0
Mortality	0	0	0	0	0	0	3	3

Study title: Acute IV Study of ADD 234037 in Rats.

Key study findings: A single dose of lacosamide (25, 50, and 100 mg/kg) was administered intravenously to rats. The rats were observed for 14 days following dosing. The following key findings were obtained:

1. No mortality occurred following the intravenous administration of lacosamide.
2. Treatment-related clinical signs included labored breathing, reduced righting ability, limb weakness, ataxia, limb splay and flattened posture.
3. Macroscopic changes were noted in the kidney and stomach of some animals in the 50 mg/kg and 100 mg/kg treatment groups.
4. Based on clinical signs, NOEL is 25 mg/kg.

Study №: Report No. 18566-0-800

Volume #, and page #: 4.2.3.1.5 b(4)
Conducting laboratory and location: ——

Date of study initiation: May 6, 1997
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: ADD 234037, Lot № PEH-A-170, % purity not stated

Methods

Doses: 25, 50, and 100 mg/kg
Species/strain: Rat/Sprague Dawley®SD®
Number/sex/group or time point (main study): 5/males/group (1 & 2); 2/sex/group (3)
Route, formulation, volume, and infusion rate: Intravenous, Solution, 1.7, 3.3, and 6.7 mL/kg to achieve the desired dose of 25, 50, and 100 mg/kg, respectively, 2 mL/minute
Satellite groups used for toxicokinetics or recovery: None
Age: approximately 8-weeks
Weight: 225 to 264 g
Sampling times: N/A

Unique study design or methodology (if any): None

Observations and times:
Mortality: Mortality was examined twice daily (4 hours apart).
Clinical signs: Clinical signs were observed immediately, approximately 15, and 30 minutes and 1, 2, and 4 hours after dosing (Day 0); and once daily thereafter until the day of termination (Day 15).
Body weights: Body weight was recorded pre-dosing on the day of dosing (Day 0), and on days 3, 7, and 14, and at termination (Day 15) than weekly until end of study.
Food consumption: Not monitored
Ophthalmoscopy: Not performed
EKG: Not performed
Hematology: Not performed
Clinical chemistry: Not performed
Urinalysis: Not performed
Gross pathology: Surviving animals were anesthetized with sodium pentobarbital, and exsanguinated. Macroscopic evaluation was performed on the cervical, thoracic and viscera.
Organ weights: Not performed
Histopathology: Not performed

Results

Mortality: No treatment-related deaths occurred; all animals survived until schedule study termination.

Clinical signs: Treatment-related clinical signs were dose-dependent. No treatment-related clinical signs were observed in the low-dose group (25 mg/kg). As indicated in the table 4 below, labored respiration, flattened posture, ataxia, loss of righting reflex, apparent hind limb weakness, slight splay in all limbs, no righting ability, prostrate and positive response to toe pinch and palpebral response were the primary treatment-related clinical signs. The onset and duration of the clinical signs were dose dependent. Compared to the mid-dose group (50 mg/kg), the onset of the clinical signs were rapid in the high dose group. The duration of effect was longer in the high dose group, with some clinical symptoms lasting up to 2 hours post-dosing. In the mid-dose group, the onset of the clinical signs began 15 minutes post-dosing. All animals appeared normal by the 2 hour post-dosing observation time.

Table 4 .Incidence of treatment-related clinical signs.

	Dose (# animals in group)																	
	25 mg/kg (n=2)						50 mg/kg (n=5)						100 mg/kg (n=5)					
	Time of Observation After Dosing																	
Symptoms	IPD	15'	30'	1hr	2hr	4hr	IPD	15'	30'	1hr	2hr	4hr	IPD	15'	30'	1hr	2hr	4hr
Normal	2	2	2	2	2	2	5	0	0	0	5	5	1	0	0	0	0	0
Labored Respiration	0	0	0	0	0	0	0	5	5	1	0	0	4	5	5	5	4	1
Flatten Posture	0	0	0	0	0	0	0	5	4	3	0	0	5	0	0	0	5	1
Ataxia	0	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0
Loss of Righting	0	0	0	0	0	0	0	1	0	0	0	0	3	0	0	0	1	0

Reflex																		
Apparent weakness in hind limb	0	0	0	0	0	0	0	1	2	3	0	0	0	0	0	0	0	1
Slight Limb splay- all limbs	0	0	0	0	0	0	0	0	2	5	0	0	0	0	0	0	0	4
Weakness in all limbs	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	5	1
Gasping	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
No Righting ability	0	0	0	0	0	0	0	0	0	0	0	0	2	5	5	5	0	0
Prostrate	0	0	0	0	0	0	0	0	0	0	0	0	0	4	5	5	0	0
Positive response to toe pinch and palpebral response	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5	5	5	2

IPD: Immediately post-dosing

Body weights: No treatment-related effects on body weight were noted.

Gross pathology: At necropsy, all animals were observed for identifying macroscopic lesions. Macroscopic changes were observed in the kidneys and stomach of some of the animals in the mid- and high-dose groups. Discoloration of the kidneys was observed in 2 and 3 animals in the mid- and high-dose groups, respectively. Lesions in the nonglandular stomach (thin and translucent circular areas) were noted in 2 animals in the mid-dose and 2 in the high-dose groups.

2.6.6.3 Repeat-dose toxicity

Study title: 13-week Subchronic Toxicity of SPM 927 by Oral Administration to CD-1 Mice.

Key study findings: Lacosamide (0.0, 30, 60, 120, and 180 mg/kg/day) was administered via gavage to mice for 13 weeks with the following results:

1. Absorption was rapid (T_{max} was between 0.5 and 1.0 hours) and AUC and C_{max} was dose-dependent. Increase in the exposure was noted with increasing doses; however, the increase was less than dose proportional. A gender difference was also observed; systemic exposure was higher in the males than the females at 120, and 180 mg/kg doses. Accumulation was observed at the two highest doses (120 and 180 mg/kg/day) in the males.
2. No treatment-related mortalities were observed in the 30, 60 and 120 mg/kg treatment groups. Two animals died in the high (180 mg/kg) group.
3. Ataxia, abdominal position and reduced motility were the primary treatment-related clinical signs. Ataxia, reduced motility and abdominal position were observed on almost all days following dosing with 120 and 180 mg/kg of lacosamide.
4. No treatment-related macroscopic or histological changes were noted.
5. Based on the clinical signs not considered to be a significant safety issues, NOAEL (in agreement with the Sponsor) is 60 mg/kg (HED = 4.9 mg/kg). This corresponds to AUD value of 97.0 μg·h/mL in males on day 91. C_{max} values at this dose on day were 29.04 (males) and 27.62 (females) μg/mL.

b(4)

Study no.: Report № —— 13123/00
Volume #, and page #: Electronic document
Conducting laboratory and location: ——— b(4)

Date of study initiation: June 21, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № KK 02457, 99.67%

Methods

Doses: 0, 30, 60, 120, and 180 mg/kg b(4)
Species/strain: Mice/CD-1/— CD®-1(ICR)BR
Number/sex/group or time point (main study): 10/sex/group

Group	Test Article	Dosage Level (mg/kg/day)	Dosage Volume (mL/kg)	Number of Animals	
				Females	Males
Main Study					
1	SPM 927	0	10.0	10	10
2	SPM 927	30	10.0	10	10
3	SPM 927	60	10.0	10	10
4	SPM 927	120	10.0	10	10
5	SPM 927	180	10.0	10	10
TK Study					
6	SPM 927	30	10.0	18	18
7	SPM 927	60	10.0	18	18
8	SPM 927	120	10.0	18	18
9	SPM 927	180	10.0	18	18

Route, formulation, volume, and infusion rate: Oral (gavage), Solution, 10.0 mL/kg
Satellite groups used for toxicokinetics or recovery: Yes: Satellite groups were used for toxicokinetic evaluation.
Age: Males: 37 days; Females: 58 days
Weight: Males: 23.5 – 25.9 g; Females: 23.4 – 25.9 g
Sampling times: See below.
Unique study design or methodology (if any): N/A

Observations and times:

Toxicokinetics: Blood samples were collected on treatment day 1 and treatment week 13 for toxicokinetic evaluation at 0.5, 1, 2, 4, 8, and 24 hours after dosing. Blood from 3 animals per sampling time was pooled.
Mortality: Mortality was examined twice daily (early morning and afternoon), except on weekends the second check was conducted at mid-day.

Clinical signs: Clinical signs were examined daily. All subjects were examined immediately after dosing and checked regularly throughout the work day from 7:30 a.m. to 4:30 p.m.
Body weights: **Pre-Dosing Period:** Body weights were recorded at the time of allocation of the subjects to their respective treatment group. **Treatment Phase:** Body weights were recorded on the day of commencement of treatment and once weekly thereafter. Body weights were recorded on the same day of the week throughout the treatment period.
Food consumption: Food consumption was recorded weekly throughout the treatment period. Weekly food consumption (g/kg b.w./day) was defined as:

Total food given (g) – Total food left (g)/# of animal days x body weight (kg)

Ophthalmoscopy: Eyes of all animals were examined before the first dose and at the end of the 13-week treatment (test day 92). During the examination of the eye, the following ocular structures were examined: adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus.
EKG: Not performed
Hematology: Blood was collected at the end of the treatment period (day 91) in the first 5/animals/sex/group in the main study. The following parameters were examined: hemoglobin (HGB), erythrocytes, leucocytes, hematocrit % (HCT%), platelet count (PLT), reticulocytes (RET; % of the erythrocytes), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), activated partial thromboplastin time (aPTT), thromboplastin time (TPT), and differential blood count.
Clinical chemistry: The following parameters were measured at the end of the treatment period (day 91) in the second 5/animals/sex/group in the main study: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphorus (PHOS), urea in blood (UN), glucose (GLU), total cholesterol (CHOL), creatinine (CREA), total protein (TP), albumin (ALB), globulin (GLOB), albumin/globulin ratio (AGR), alkaline phosphatase (ALP), aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), lactate dehydrogenase (LDH) and total bilirubin (TBIL).
Urinalysis: Not performed
Gross pathology: At necropsy
Organ weights: The weights of the following organs were measured at necropsy in all animals: adrenal (2), brain, heart, kidney (2), liver, lungs, ovary (2), prostrate, spleen, testicle (2), thymus, and uterus.
Histopathology: The following tissues were collected from all animals at necropsy and those that died during the study:

Dose (mg/kg)	**0**	**30**	**60**	**120**	**180**
Species	**Mice**				
Adrenals	X	X	X	X	X
Aorta					
Bone Marrow smear					
Bone (femur)					
Brain (cerebrum, cerebellum, brain stem)	X	X	X	X	X
Cecum					

Cervix	X	X	X	X	X
Colon					
Duodenum					
Epididymis					
Esophagus					
Eye					
Fallopian tube					
Gall bladder					
Gross lesions					
Harderian gland					
Heart (left & right ventricles, septum)	X	X	X	X	X
Ileum					
Injection site					
Jejunum					
Kidneys (and ureter)	X	X	X	X	X
Lachrymal gland					
Larynx					
Liver	X	X	X	X	X
Lungs (with mainstem bronchi & bronchioles)	X	X	X	X	X
Lymph nodes, cervical					
Lymph nodes mandibular					
Lymph nodes, mesenteric					
Mammary Gland					
Nasal cavity					
Optic nerves					
Ovaries	X	X	X	X	X
Pancreas					
Parathyroid					
Peripheral nerve					
Pharynx					
Pituitary					
Prostate	X	X	X	X	X
Rectum					
Salivary gland					
Sciatic nerve					
Seminal vesicles					
Skeletal muscle					
Skin					
Spinal cord					
Spleen	X	X	X	X	X
Sternum					
Stomach					
Testes	X	X	X	X	X
Thymus	X	X	X	X	X
Thyroid					
Tongue					

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Trachea					
Urinary bladder					
Uterus (incl. Oviducts)	X	X	X	X	X
Vagina					
Zymbal gland					

Tissues were fixed in 7% buffered formalin. Tissues from the control and high-dose groups were stained with hematoxylin and eosin stain and examined histologically. In addition, frozen sections of the heart, liver and kidney (2) were prepared, stained with scarlet red and examined histologically for the presence of fat infiltration. The liver of animals in all treatment groups was examined for fatty infiltration. Also, macroscopic lesions were examined microscopically from each animal in the low- and mid-dose groups.

Adequate Battery: yes (x), no ( )—explain Although the full histopathology panel of tissues was not examined in this report, this study was employed as the dose range-finding study for the carcinogenicity protocols and was not necessary as a pivotal study to support the chronic indication (rat and dog studies were the pivotal chronic studies).

Peer review: yes (x), no ( )

Results

Toxicokinetics: Blood samples were collected on treatment day 1 and treatment week 13 at 0.5, 1, 2, 4, 8, and 24 hours after dosing. Blood from 3 animals per sampling time was pooled.

Toxicokinetic analysis is presented in Table 1 below. Mean peak plasma level were generally obtained at 0.5 hours after dosing except at the highest dose (180 mg/kg/day) on day 1 for which the mean T_{max} was 1.0 hours. Systemic exposure as defined by the C_{max} and $AUC_{0-24)}$ values increased with dose in a less than dose proportional manner on both days 1 and 91. A 6-fold increase in dose (30-180 mg/kg) resulted in a 3.2-fold and 4.8-fold increase in C_{max} in males (17.69 vs 56.06 µg/mL) and females (16.88 vs 81.48 µg/mL), respectively, on day 1. On day 91, a 2.7-fold increase (19.99 vs 53.82 µg/mL) and a 2.3-fold increase (20.38 vs 45.86 µg/mL) in C_{max} was noted in males and females, respectively. $AUD_{(0-24)}$ values increased in a dose proportional manner on day 1 for both males (47.9 vs 269.1 µg/mL) and females (58.8 vs 361.5 µg/mL). On day 91, $AUC_{(0-24)}$ for males (6.1-fold, 51.5 vs 314.6 µg/mL) increased in a dose proportional manner; whereas in females (5.2-fold, 46.2 vs 240.2 µg/mL) a less than proportional increase was noted. Systemic exposure appears to be different between males and females. As depicted in the table 2 below (table 5 as copied from the Sponsor's submission), on day 91, the exposure (C_{max}) tended to be higher in the males than the females at the two higher doses and less at the lower doses. Compared to the female animals, accumulation of lacosamide was noted in the males; a 1.2-fold accumulation was noted at the two highest doses. At the two lower doses (30 and 60 mg/kg), a 1.0-fold increase accumulation was noted.

Table 1. Mean toxicokinetic parameters after oral administration of lacosamide on Study Day 1 and Study Day 91.

Study Day	Dose (mg/kg/day)	Sex	T_{max} (hr)	C_{max} (µg/mL)	AUC (µg·h/mL)
1	30.0	M	0.5	17.69	47.9
	30.0	F	0.5	16.88	58.8
	60.0	M	0.5	26.86	95.1
	60.0	F	0.5	24.70	96.5
	120.0	M	1.0	40.84	188.6
	120.0	F	0.5	46.34	204.8
	180.0	M	1.0	56.06	269.1
	180.0	F	1.0	81.48	361.5
91	30.0	M	0.5	19.9	51.5
	30.0	F	0.5	20.38	46.2
	60.0	M	0.5	29.04	97.0
	60.0	F	0.5	27.62	131.3
	120.0	M	0.5	42.42	228.8
	120.0	F	0.5	36.64	170.4
	180.0	M	0.5	53.8	314.6
	180.0	F	0.5	45.86	240.2

Table 2. Ratios of lacosamide plasma concentration and toxicokinetic parameters on Day 91:Day 1

	Ratio Day 91:Day 1							
Time (hr)	30 mg/kg		60 mg/kg		120 mg/kg		180 mg/kg	
	M	F	M	F	M	F	M	F
0.5	1.13	1.21	1.08	1.12	1.22	0.79	0.99	0.63
1	0.97	0.91	1.11	0.97	0.85	1.07	0.71	0.56
2	1.08	0.76	1.15	0.64	0.88	0.71	0.77	0.57
4	1.08	0.56	1.12	0.85	1.34	0.78	1.04	0.75
8	1.41	0.96	0.64	6.40	1.51	0.89	2.03	0.90
24	1.40	2.49	1.69	2.63	1.89	0.36	0.06	0.02
C_{max} (µg/mL)	1.13	1.21	1.08	1.12	1.05	0.79	0.96	0.56
$AUC_{(0-24)}$ (µg·h/mL)	1.08	0.79	1.02	1.36	1.21	0.83	1.17	0.66

Mortality: No treatment-related deaths were noted in the 30, 60, and 120 mg/kg treatment groups. Two animals in the high-dose group died during the study. One male died on Day 67; macroscopic findings were noted in the spleen at necropsy. These findings included a markedly swollen and enlarged spleen (size: 4.5 x 1.5 x 1 cm). On study Day 84, one female died. Macroscopic finding noted at necropsy included a markedly enlarged thymus.

Clinical signs: No treatment-related effects were observed in the 30 mg/kg/day group. Ataxia, abdominal position, and reduced motility were the primary treatment-related clinical signs observed (Table 3). These clinical signs occurred 10 minutes after dosing. Their duration of effect was dose-dependent; lasting for 1 hour following the 60 and 120 mg/kg doses and from 3 to 4 hours after the high dose (180 mg/kg). In contrast to ataxia which occurred on the first 2 days of dosing in all animal; reduced motility did not occur until day 16 of dosing; and was observed in all animals until the termination of the study.

Table 3. Primary clinical signs observed in the mice following oral dosing with lacosamide.

Clinical Sign	Dose (mg/kg)	Observation
		Males
	0	No clinical signs noted
	30	No mortality No treatment-related clinical signs
Ataxia	60	D1 and D2: all animals displayed slight ataxia 10-mins after dosing that lasted for 1 hour.
Ataxia	120	D1-D91: All (D1-11; D14, D15, D29- 91) to several (D12, D13, D16-D28) animals displayed ataxia from the first day of dosing (D1) to termination (D91)
Abdominal Position		Several animals (1 to 7) displayed abdominal position 10-min after dosing from day 12 until termination of the study on day 91. The abdominal position lasted 1 to 2 hours after dosing.
Apathy		D12 and D13: 3/10 animals displayed apathy
Reduced Motility		D16- D91: All animals displayed reduced motility within 10 minutes after dosing and lasting from 1 to 2 hours.
Death	180	D67: One subject died
Ataxia		D1; D15; D20-D23; D28-91: all animals were ataxia 10-mins after dosing; lasting for 3 to 4 hrs. D16-D19; D24-D27: several animals (4-9) were ataxia 10 mins after dosing; lasting 3 to 4 hours.
Abdominal Position		Several animals to all animals displayed abdominal position 10-min after dosing on D1 (n=10), D2 (n=10) and from D12 (1-10) until termination of the study on day 91. The abdominal position lasted 3 to 4 hours after dosing.
Reduced Motility		D16- D91: All animals displayed reduced motility within 10 minutes after dosing and lasting from 3 to 4 hours.
		Females
	0	No clinical signs noted

	30	No mortality No treatment-related clinical signs
Ataxia	60	D1 and D2: all animals displayed slight ataxia 10-mins after dosing that lasted for 1 hour. On D13 and D14, 3/10 and 2/10 females was ataxia
Ataxia		D1-D11; D14; D15; D29-91: All females were ataxic 10-mins after dosing; lasting 1 hr. On D13 and D14 , 3/10 and 2/10 females were ataxic
Abdominal Position	120	Several animals (1 to 8) displayed abdominal position 10-min after dosing from day 12 until termination of the study on day 91. The abdominal position lasted 1 to 2 hours after dosing.
Reduced Motility		D16- D91: All animals displayed reduced motility within 10 minutes after dosing and lasting for 1 hour.
Death		D67: one death was reported
Ataxia		D1-D11; D14; D15; D29-91: all animals were ataxia 10-mins after dosing; lasting for 3 to 4 hrs. D13; D18; D20-D28: several animals (1-6) were ataxia 10 min after dosing; lasting 3 to 4 hours.
Abdominal Position	180	D12-D15; D30-D91: Several animals to all animals displayed abdominal position 10-min after dosing on. The abdominal position lasted 3 to 4 hours after dosing.
Reduced Motility		D16-D91: All animals displayed reduced motility within 10 minutes after dosing and lasting from 3 to 4 hours

Body weights: No treatment-related changes in body weights were observed.

Food consumption: No treatment-related changes in food consumption were observed.

Ophthalmoscopy: No treatment-related changes were noted in the eye or the following ocular structures: adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus.

EKG: Not performed

Hematology: The standard battery of hematological parameters was assessed on Day 91 for the first 5/animals/sex/group in the main study. No treatment-related changes were noted in the hematology parameters measured.

Clinical chemistry: Clinical chemistry parameters were assessed on Day 91 for the second 5/animals/group in the main study. No treatment-related changes were noted in the chemistry parameters measured.

Urinalysis: Not performed.

Gross pathology: At necropsy, all animals were observed for identifying macroscopic lesions. No treatment-related macroscopic changes were identified. In the two animals that died during the treatment period some macroscopic changes were noted. These changes are presented in the table below:

Dose (mg/kg)	Animal № (sex)	Day of Death	Macroscopic post mortem finding
180	84 (Male)	Day 67	**Spleen**: Markedly swollen and enlarged (size: 4.5 x 1.5 x 1 cm)
180	94 (Female)	Day 84	**Thymus**: Markedly enlarged

Organ weights: Compared to control, there were no treatment-related effects on absolute or relative organ weight.

Histopathology: No treatment-related histological findings were observed.

Study title: 13-week Oral Gavage Subchronic Toxicity Study of ADD 234037 in Rats.

Key study findings: Lacosamide (0.0, 30 100, and 300 mg/kg/day) was administered via gavage to rats for 13 weeks with the following results:

1. Absorption was rapid (T_{max} was between 0.5 and 2.0 hours) and AUC and C_{max} was dose-dependent. Increase in the exposure was noted with increasing doses; however, the increase was less than dose proportional.
2. Treatment-related mortalities were observed in the 300 mg/kg female treatment groups. The cause of these deaths was not evident histologically.
3. Treatment-related clinical signs included ataxia, hypoactivity, prostration, dyspnea and convulsions. Convulsions were only observed in the females.
4. No treatment-related macroscopic or histological changes were noted. However, both light and electron microscopy evaluation of the liver from the females in the high dose group did show changes in the liver. In comparison to controls, light microscopy revealed minimal to moderate hypertrophy of hepatocytes in all females evaluated. Electron microscopy revealed hypertrophy of hepatocytes with increases in number of mitochondria and rough endoplasmic reticulum in the cytoplasm of hepatocytes in comparison to control. No degenerative changes in cellular organelles of hepatocytes were noted in the high dose females. These changes are most likely the result of the observed increase in ALT and alkaline phosphatase.
5. Statistically significant alterations of uncertain toxicological significance was observed in some of the hematology chemistry parameters in both male and female rats, primarily at the 300 mg/kg/day level.
6. Changes in urine chemistry indicate that lacosamide has diuretic-like effect. Significant increases in urine volume were observed in both male and females starting at the lowest dose (30 mg/kg/day).

7. Based on the clinical signs not considered to be a significant safety issues, NOAEL (in agreement with the Sponsor) is 100 mg/kg (HED = 4.9 mg/kg). This corresponds to AUC value of 171595 and 228815 ng.h/mL in males and females, respectively, on day 91. C_{max} values at this dose on day 91 were 27033 (males) and 36033 (females) ng/mL.

b(4)

Study no.: — **Report № 148-235**
Volume #, and page #: Electronic document
Conducting laboratory and location: — b(4)

Date of study initiation: April 24, 1997
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: ADD 234037, Lot № PEH-A-170, 100% (assumed)

Methods

Doses: 0, 30, 100 and 300 mg/kg
Species/strain: Rats/Hsd:Sprague-Dawley® SD®
Number/sex/group or time point (main study): 15/sex/group

Group	Test Article	Dosage Level (mg/kg/day)	Dosage Concentration (mg/mL)	Dosage Volume (mL/kg)	Number of Animals	
					Females	Males
Main						
1	AD 234037	0	0	5.0.	15	15
2	AD 234037	30	6	5.0	15	15
3	AD 234037	100	20	5.0	15	15
4	AD 234037	300	60	5.0	15	15
Satellite						
2	AD 234037	30	6	5.0	18	18
3	AD 234037	100	20	5.0	18	18
4	AD 234037	300	60	5.0	18	18

Route, formulation, volume, and infusion rate: Oral gavage, Solution, 5 mL/kg
Satellite groups used for toxicokinetics or recovery: yes; 18/sex/group
Age: 7 weeks
Weight: Males: 157.0 to 189.0 g; Females: 135.0 to 159.0 g
Sampling times: See below.
Unique study design or methodology (if any): None.

Toxicokinetics: Blood samples were collected on day 1 and day 91 (prior to termination) for toxicokinetic evaluation. On day 1 blood was collected at 0 (prior to dosing), 0.5, 1, 2, 4, and 8 hours after dosing from 3 animals/sex/group. On day 91, blood was collected at 0 (prior to dosing), 1, 2, 4 and 8 hours after dosing from 3 animals/sex/group per sampling time.

Mortality: Mortality was examined twice daily (morning and afternoon, at least 6 hours apart).

Clinical signs: Clinical signs were examined twice daily. All subjects were examined during the morning mortality check and approximately one hour after dosing.
Body weights: Body weights were recorded at randomization, prior to treatment and weekly thereafter.
Food consumption: Food consumption was recorded weekly.
Ophthalmoscopy: An indirect ophthalmic examination was recorded weekly.
EKG: Not performed
Hematology: Blood was collected during week 14 (prior to necropsy). The following parameters were examined: hemoglobin (HGB), erythrocytes, leucocytes, hematocrit % (HCT%), platelet count (PLT), reticulocytes (RET; % of the erythrocytes), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), activated partial thromboplastin time (aPTT), prothrombin time (PT), differential blood cell count, and blood cell morphology
Clinical chemistry: The following parameters were measured during week 14 (prior to necropsy): sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphorus (PHOS), urea nitrogen (UN), glucose (GLU), cholesterol (CHOL), creatinine (CREA), total protein (TP), albumin (ALB), globulin (GLOB), albumin/globulin ratio (AGR), alkaline phosphatase (ALP), aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), gamma glutamyltransferase, tricyclerides, and total bilirubin (TBIL).
Urinalysis: Prior to collection of blood during week 14, urine was collected during the overnight fast (at least 20 hours). The following parameters were evaluated: total volume, specific gravity, pH, bilirubin, occult blood, protein, ketones, glucose, urobilinogen, appearance, color, and sediments (microscopic examination).
Gross pathology: Surviving animals were anesthetized with sodium pentobarbital, and exsanguinated. Macroscopic evaluation was performed on all orifices, external surface of the body, nasal cavity and paranasal sinuses, cranial cavity, external surfaces of the brain and spinal cord, cervical tissues and organs, thoracic, abdominal, and pelvic cavities and viscera.
Organ weights: The weights of the following organs were measured at necropsy in all animals: adrenal (2), brain, heart, kidney (2), liver, ovary (2), pituitary (post fixation), spleen, testis with epididymis (2), thyroids/parathyroids (post fixation), and thymus.

Histopathology: The following tissues were collected from all animals at necropsy and those that died during the study:

Dose (mg/kg)	**0**	**30**	**100**	**300**
Species	**Rats**			
Adrenals	X	X	X	X
Aorta	X	X	X	X
Bone Marrow smear (femur)	X	X	X	X
Bone (femur)	X	X	X	X
Brain (cerebrum, cerebellum, brain stem)	X	X	X	X
Cecum	X	X	X	X
Cervix	X	X	X	X

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Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis	X	X	X	X
Esophagus	X	X	X	X
Eye (2)	X	X	X	X
Fallopian tube	X	X	X	X
Gall bladder				
Gross lesions	X	X	X	X
Harderian gland				
Heart (left & right ventricles, septum)	X	X	X	X
Ileum	X	X	X	X
Injection site				
Jejunum	X	X	X	X
Kidneys (and ureter)	X	X	X	X
Lachrymal gland				
Larynx				
Liver	X	X	X	X
Lungs (with main stem bronchi & bronchioles)	X	X	X	X
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric	X	X	X	X
Mammary Gland	X	X	X	X
Nasal cavity				
Optic nerves	X	X	X	X
Ovaries with fallopian tubes	X	X	X	X
Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve				
Pharynx				
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum				
Salivary gland (mandibular)	X	X	X	X
Sciatic nerve	X	X	X	X
Seminal vesicles (2)	X	X	X	X
Skeletal muscle (thigh)	X	X	X	X
Skin (abdomen)	X	X	X	X
Spinal cord				
Spleen	X	X	X	X
Sternum				
Stomach	X	X	X	X
Testes	X	X	X	X
Thymus	X	X	X	X
Thyroid (2) with parathyroid	X	X	X	X

Tongue				
Trachea	X	X	X	X
Urinary bladder	X	X	X	X
Uterus	X	X	X	X
Vagina	X	X	X	X
Zymbal gland				

Tissues were fixed in 10% neutral-buffered formalin. Tissues from the control and high-dose groups and from all animals that died were stained with hematoxylin and eosin stain and examined histologically. Also, the lung, liver, and gross lesions were examined microscopically from all animals in group 2 (30 mg/kg) and 3 (100 mg/kg).

Adequate Battery: yes (X), no ( )—explain
Peer review: yes (x), no ( )

Results

Toxicokinetics: Toxicokinetic analysis is presented in Table 1 below. Mean peak plasma level were generally obtained at 0.5 to 2 hours after dosing. Systemic exposure as defined by the C_{max} and $AUC_{(0-24)}$ values increased with dose in a less than dose proportional manner on both days 1 and 91. A 3-fold increase in dose (30-100 mg/kg) resulted in a 2-fold and 1.7-fold increase in C_{max} in males (21833 vs 10680 ng/mL) and females (21967 vs 12967 µg/mL), respectively, on day 1. On day 91, a 2.3-fold increase (27033 vs 11967 ng/mL) and a 2.5-fold increase (36033 vs 14433 ng/mL) in C_{max} was noted in males and females, respectively. $AUC_{(0-24)}$ values also increased in a less than dose proportional manner on day 1 for both males (2.3-fold, 62376 vs 146616 ng.hr/mL) and females (1.9-fold, 78326 vs 152392 ng.hr/mL). A 10-fold increase in dose (30 vs 300 mg/kg) also resulted in an increase in both Cmax and AUC a less than proportional manner.

Table 1. Mean toxicokinetic parameters after oral administration of lacosamide on Study Day 1 and Study Day 91.

Study Day	Dose (mg/kg/day)	Sex	T_{max} (hr)	C_{max} (ng/mL)	AUC (ng.h/mL)
1	30.0	M	0.5	10680	62376
	30.0	F	1.0.	12967	78326
	100.0	M	0.5	21833	146616
	100.0	F	1.0	21967	152392
	300.0	M	1.0	34233	218433
	300.0	F	2.0	40333	216169
91	30.0	M	1.0	11967	61298
	30.0	F	1.0	14433	36033
	100.0	M	2.0	27033	171595
	100.0	F	1.0	36033	228815

	300.0	M	1.0	57633	340052
	300.0	F	1.0	57100	408105

Mortality: No treatment-related deaths were observed in the low- and mid-dose groups. Five females in high-dose group died during the study. Two females died during week 2, 2 females died during week 3, and one female died during week 11. The female that died during week 11 was observing having signs of dyspnea two days prior to her death. The Sponsor stated that no gross pathology could be correlated to the deaths; hence the cause of death in these animals was undetermined.

Clinical signs: No treatment-related effects were observed in the low- and mid-dose groups. Ataxia, hypoactivity, and dyspnea were the primary treatment-related clinical signs observed in both genders (Table 1). Female animals also displayed convulsions and the feeling of cold to touch. No clear distinct pattern was discernible with respect to the onset, severity, and incidence for the ataxia, hypoactivity and prostration. Dyspnea was observed only during the first two weeks of study. Convulsion was observed on day 12 or 15 in the females.

Table 1. Primary clinical signs observed in rats following oral dosing with lacosamide.

Clinical Sign	Dose (mg/kg)	Observation
		Males
	0	No clinical signs noted
	30	No mortality No treatment-related clinical signs
	100	No treatment-related clinical signs noted. No mortality
Head tilt		1 Animal on D36, D43 and D44
Ataxia		N = 14 (Post-dosing):
Hypoactive	300	N = 4
Hyperactive		N = 15
Dyspnea		N = 3
Prostrate		N = 4
		Females
	0	No clinical signs noted
	30	No mortality No treatment-related clinical signs
	100	No mortality No treatment-related clinical signs
Ataxia		N = 15
Death		N = 5; Week 2 (n=2), Week 3 (n=1), Week 11 (n=2)
Ataxia		N = 15; immediately after dosing
Cold to touch		N = 5;

Convulsions	300	N = 3; post-dosing on D12 (n=2) and D15 (n=1)
Hypoactive		N = 15
Hyperactive		N = 1
Prostrate		N = 7
Tremors		N = 1
Dyspnea		N = 14

Body weights: Body weight was measured prior to dosing and weekly for 14-weeks. Mean weekly body gain is presented in the table below. Statistically significant increases and decreases in body weight gain were sporadically noted between lacosamide-treated groups and controls during the study. These were considered incidental as they were not clearly dose-related or found consistently throughout the study.
Body weight gain by the end of the study was affected by treatment with lacosamide in males in the low-dose group and females in the low- and mid-dose groups when compared with body weight gain of vehicle treated animals.

Table 2. Mean Body Weight Gain in Rats treated with lacosamide for 13 weeks.

	Mean Body Weight Gain in g ± S.D. (% of control)							
Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	30	100	300	0	30	100	300
1	37 ± 5.4	37 ± 5.3	41 ± 6.0 (+10.8%)	29 ± 6.3 (-21.6%)*	11 ± 9.8	17 ± 4.8 (+54.5%)	14 ± 9.5 (+27%)	16 ± 11.9 (+45.5%)
2	33 ± 6.2	34 ± 4.5 (+3.0%)	36 ± 5 (+9.1%)	38 ± 5.9 (+15.2%)	19 ± 8.7	25 ± 10.7 (+31.6%)	17 ± 7.9 (-10.5%)	16 ± 5.6 (-15.8%)
3	21 ± 4.7	23 ± 3.9 (+9.5%)	25 ± 7.2 (+19%)	13 ± 17.2 (-38.1%)	9 ± 5.5	8 ± 11.2 (-11.1%)	12 ± 7.2 (+33.3%)	9 ± 6.8 (-)
4	23 ± 6.0	23 ± 4.1 (-)	27 ± 4.4 (+17.4%)	24 ± 8.0 (+4.3%)	15 ± 11.2	13 ± 8.1 (13.3%)	10 ± 6.6 (-33.3%)	10 ± 19.1 (-33.3%)
5	15 ± 4.8	16 ± 3.2 (+6.7%)	18 ± 4.1 (+20%)	15 ± 5.2 (-)	2 ± 9.3	6 ± 8.4 (+200%)	8 ± 7.2 (+300%)	8 ± 5.1 (+300%)
6	18 ± 5.0	17 ± 2.7 (-5.6%)	20 ± 6.7 (+11.1%)	17 ± 5.3 (-5.6%)	9 ± 9.4	11 ± 9.5 (+22.2%)	8 ± 9.4 (-11.1%)	15 ± 13.5 (+66.7%)
7	8 ± 5.4	8 ± 4.2 (-)	10 ± 2.7 (+25%)	10 ± 6.6 (+25%)	-1 ± 6.4	2 ± 6.5 (-)	8 ± 9.4 (+400%)*	0 ± 7.5 (-)
8	15 ± 2.8	15 ± 4.1 (-)	15 ± 4.1 (-)	12 ± 6.6 (-20%)	11 ± 7.8	9 ± 6.1 (+18.2%)	11 ± 6.9 (-)	9 ± 5.0 (-18.2%)
9	6 ± 4.4	8 ± 5.0 (+33.3%)	7 ± 6.1 (+16.7%)	6 ± 5.0 (-)	0 ± 6.9	2 ± 6.3 (+4.9%)	0 ± 7.2 (-)	4 ± 6.8 (+4.0%)
10	10 ± 3.2	10± 3.8 (-)	12 ± 4.5 (+20%)	8 ± 3.7 (-20%)	7 ± 5.0	4 ± 7.2 (-42.9%)	4 ± 7.2 (-42%)	4 ± 8.9 (-42%)
11	4 ± 5.5	6 ± 5.9 (+50%)	3 ± 4 (-25%)	4 ± 4.8 (-)	1 ± 4.5	2 ± 7.4 (+100%)	5 ± 4.9 (+400%)	2 ± 6.0 (+100%)
12	7 ± 3.9	9 ± 6.7 (+29%)	12 ± 3.7 (+71%)	7 ± 4.9 (-)	0 ± 5.4	4 ± 4.9 (-)	8 ± 6.7 (+100%)*	4 ± 5.8 (+)
13	-1 ± 4.4	0 ± 5.1 (-)	-1 ± 4.0 (-)	-1 ± 4.8 (-)	0 ± 6.7	-2 ± 4.9 (-)	-2 ± 6. 0 (-%)	1 ± 6.4 (-%)
1 - 13	196 ± 22.0	206 ± 21.4 (+5.1%)	225 ± 33.2 (+14.8%)*	182 ± 31.0 (-7.1%)	85 ± 15.1	102 ± 13.3 (+20%)*	100 ± 16.5 (+11.6%)	95 ± 16.4 (+11.8%)*

*: Significantly different from control group at $p \leq 0.05$

Food consumption: Significant reduction in food consumption was observed in the male high dose group during week 1. Significant increase in food consumption was observed in the mid-dose males during weeks 4 thru 8 and 12. Females in all treatment groups had a significant increase in food consumption during week 7.

Ophthalmoscopy: No treatment-related effects were observed.

EKG: Not performed.

Hematology: Hematology parameters were assessed during week 14 (prior to necropsy) in the animals in the main study. Statistically significant changes in mean erythroid and, leukocytes parameters were observed. Changes in the mean erythroid parameters included a statistically slight significant increase in mean cell volume (MCV) and mean cell hemoglobin (MCH). In 300 mg/kg/day males, the MCV and MCH were increased by 3.0% and 2.7% compared to the control group, respectively. Relative to control, the mean cell hemoglobin was significantly increased by 2.6% and 3.1% in females at 100 and 300 mg/kg/day, respectively. In high dose females, segmented neutrophils were significantly increased by 100% compared to control. Overall, the results indicated that were no apparent biologically significant test article effects on hematological parameters under the tested conditions.

Clinical chemistry: Treatment-related effects on alkaline phosphatase, total cholesterol, triglycerides, alanine aminotransferase, calcium, inorganic phosphorus, urea nitrogen and chloride. Statistically significant changes noted at the week 14 blood draws are summarized in the table below. Minor treatment-related decrease in aspartate aminotransferase was observed in the females in the 30 mg/kg/day group. Most notable observations were noted in alklanine phosphatase (ALKP), alanine aminotransferase and total cholesterol triglycerides. A dose-dependent increase in ALKP was noted in females; at 100 and 300 mg/kg/day, ALKP was significantly higher than control value by 41% and 44%, respectively. ALKP in males in 100 mg/kg/day was significantly higher than control by 20.8%. Alanine aminotransferase was statistically higher than the control in both males and females at 300 mg/kg/day (31.4% and 81.1% in males and females, respectively). A 51.45% increase in ALAT was noted in the mid-dose females. A dose-dependent increase in triglyceride plasma levels was noted in females only; compared to control, triglyceride levels were increased by 46.5% and 76.7% at a dose of 100 and 300 mg/kg/day, respectively. Total cholesterol in females at 100 mg/kg/day was statistically higher than control by 55%. Other statistically significant changes were at < 20% and were considered incidental/not toxicologically significant.

Summary of significant clinical findings following oral administration of lacosamide.

		Dose (mg/kg/day)			
Parameter	**Gender**	**0**	**30**	**100**	**300**
Urea Nitrogen (mg/dL)	Males	18.0 ± 3.3	18.0 ± 2.4	17.0 ± 2.1 (-5.5%)	19.0 ± 3.6 (+5.6%)
	Female	19.0 ± 2.3	18.0 ± 3.0	17.0 ± 2.5*	16.0 ± 1.6*

			(-5.3%)	(-11.0%)	(-16.0%)
Alkaline Phosphatase (U/L)	Males	83.0 ± 14.1	87.0 ± 17.7 (+ 4.8%)	100.0 ± 15.0* (+20.5%)	112.0 ± 13.9* (+35%)
	Females	66.0 ± 12.6	74.0 ± 13.6 (+15%)	93.0 ± 26* (+41%)	95.0 ± 27.4* (+44%)
Total Cholesterol (mg/dL)	Males	96.0 ± 23.2	107.0 ± 25.9 (+11.5%)	106.0 ± 21.7 (+10.4%)	105.0 ± 18.1 (+9.4%)
	Females	80.0± 12.9	91.0 ± 26.7 (+13.8%)	124 ± 17.3* (+55%)	125.0 ± 29.2* (+56%)
Aspartate Aminotransferase (U/L)	Males	81.0 ± 7.9	73.0 ± 9.3 (-9.9%)	81.0 ± 16.3 NC	80.0 ± 9.3 (--1.2%)
	Females	84.0 ± 7.4	75.0 ± 5.7* (-11%)	74 ± 7.1* (-12%)	80.0 ± 14.3 (-4.8%)
Alanine Aminotransferase (U/L)	Males	51.0 ± 8.5	46.0 ± 7.5 (-9.8%)	57.0 ± 9.9 (+11.8%)	67.0 ± 12.3* (+31.4%)
	Females	37.0 ± 5.0	39.0 ± 4.1 (+5.4%)	56.0 ± 12.2* (+51.4%)	67.0 ± 23.0* (+81.1%)
Calcium (mg/dL)	Males	10.8 ± 0.35	10.8 ± 0.35 (NC)	10.9 ± 0.27 (+0.9%)	11.2 ± 0.31* (+3.7%)
	Females	10.7 ± 0.23	10.9 ± 0.30 (+1.9%)	11.0 ± 0.33* (+2.8%)	10.8 ± 0.47 (+0.9%)
Triglycerides (mg/dL)	Males	72.0 ± 29.3	80.0 ± 19.7 (+11.1%)	81 ± 26 (+12.5%)	80 ± 22.6 (+11.1%)
	Females	43 ± 9.4	54 ± 15.1 (+25.6%)	63.0 ± 14.7* (+46.5%)	76 ± 24.4* (+76.7%)
Inorganic Phosphorous (mg/dL)	Males	7.5 ± 0.77	7.3 ± 0.98 (-2.7%)	7.3 ± 0.71 (-2.7%)	8.2 ± 0.94 (+9.3%)
	Females	6.6 ± 0.82	7.0 ± 1.04 (+6.1%)	6.7 ± 0.90 (+1.5%)	7.8 ±0.81* (+18.2%)

*: Significant different from control value, $p \leq 0.05$ NC: No changes

Urinalysis: Treatment-related effects on urine chemistry were observed. As depicted in the table below, statistically lacosamide caused a significant decrease in mean value for urinary urea, nitrogen, creatinine, sodium and potassium. Also, lacosamide significantly increased urine volume. In addition, the urine of the treated animals was more diluted, pale in color and had a slightly lower specific gravity at the mid- and high-dose. Mean values of specific gravity was 1.038, 1.039, 1.027 and 1.021 at dose level of 0.0, 30, 100 and 300 mg/kg/day, respectively.

		Dose (mg/kg/day)			
Parameter	**Gender**	**0**	**30**	**100**	**300**
Urine Volume (mL)	Males	9.3 ± 3.46	10.3 ± 3.54 (+10.8%)	19.5 ± 6.49* (+109.7%)	29.0 ± 14.31* (+211.8)
	Female	8.5 ± 3.67	18.0 ± 7.51* (+111.8%)	30.3 ± 12.2* (+356.5)	42.6 ± 13.41** (+401.2%)
Chloride (Meq/L)	Males	103.0 ± 1.6	102.0 ± 1.8 (-1%)	102.0 ± 0.7* (-1%)	101.0 ± 1.5* (-1.9%)
	Females	104.0 ± 1.3	104 ± 1.3 (NC)	103.0 ± 2.4 (-1%)	103.0 ± 2.2* (-1%)
Urea Nitrogen (mg/dL)	Males	2468.0 ± 707.7	2414 ± 807.2* (-100%)	1421.0 ± 506.6* (-42.4%)	1128 ± 671.5* (-54.3%)
	Females	1995.0 ± 773.3	1155.0 ± 548.9* (-42%)	678 ± 292.0* (-66%)	401.0 ± 274.8* (-79.8%)
	Males	156.9 ± 42.26	156.4 ± 51.74	88.5 ± 30.95*	63.8 ± 37.84*

Creatinine (mg/dL)			NC	(-43.6%)	(-59.3%)
	Females	111.0 ± 51.54	58.8 ± 29.98*- (- 47.0%)	34.4 ± 13.01* (-69%)	21.2 ± 16.07* (-80.9%)
Sodium (Meq/L)	Males	52.5 ± 23.87	44.4 ± 18.42 (-45.3%)	28.7 ± 16.03 (-45.3%)	31.0 ± 25.71* (+31.4%)
	Females	49.4 ± 30.59	30.5 ± 17.0 (-38.3%)	15.3 ± 7.48* (-69.0%)	11.3 ± 7.78* (-77.1%)
Potassium (Meq/L)	Males	161.8 ± 52.91	159.1 ± 50.35 (-1.7%)	105.2 ± 40.44* (-35%)	89.1 ± 64.63* (-45%)
	Females	117.8 ± 54.07	75.9 ± 39.30 (-35.6%)	44.3 ± 18.66* (-62.4%)	27.0 ± 20.99* (-77.1%)
	Females	6.6 ± 0.82	7.0 ± 1.04 (+6.1%)	6.7 ± 0.90 (+1.5%)	7.8 ±0.81* (+18.2%)

*: Significant different from control value, $p \leq 0.05$ NC: No changes

Gross pathology: No treatment-related macroscopic effects were noted during the necropsy examination.

Organ weights: Statistically significant changes noted in organ weight are summarized in the table below. Most notable observation was noted in the adrenal and liver following oral administration of lacosamide. Treatment-related increase in absolute, relative-to-body weight and relative-to-brain weight were noted in both males and females at all dose levels. Liver weight change observed in females was dose-dependent. Significant increase in absolute, relative-to-body weight and relative-to-brain weight was observed in both genders at the 300 mg/kg/day dose level. The Sponsor indicated that the adrenal weight change was treatment-related and may reflect stress associated with the pharmacological effects of lacosamide. The other statistically significant changes at <20% change are considered incidental/not toxicologically significant.

		Percent Control Changes in Organ Weight					
		Males			Females		
	Dose mg/kg/day →	30	100	300	30	100	300
Organ	Parameter						
Adrenal	Absolute	+18.9%*	+20.8%*	+28.3%	+13.6%	+8.5%	+27.1%*
	Relative-to-bodyweight	+17.10%	+12.4%	+343.9%*	+8.3%	+2.5%	+22.5%*
	Relative-to-brain weight	+15.5%	+16.2%	+26.8%*	+8.8%	+4.1%	+28.6%*
Brain with stem	Absolute wt.	+1.1%	+3.7%	+0.5%	+4.6%*	+4.0%	-1.1%
	Relative-to body weight	-0.65%	-4.3%	+4.1%	-1.1%	-1.5%	-4.9%
	Relative-to-brain weight	-	-	-	-	-	-
Spleen	Absolute wt.	-1.3%	+7.6%	-3.8%	+11.3%	+13.2%*	+1.9%
	Relative-to body weight	-3.1%	-1.5%	-0.5%	+5.6%	+7.9%	-2.3%
	Relative-to-brain weight	-2.1%	+3.8%	-4.5%	+6.2%	+9.5%	+2.3%
Kidney	Absolute wt.	+2%	+11.6%*	-2.4%	+5.3%	+6.0%	+11.3%*
	Relative-to body weight	+1.3%	+3.4%	+1.6%	+0.5%	+0.3%	+7.0%*
	Relative-to-brain weight	+0.6%	+7.5%	-3.3%	+0.7%	+1.3%	+11.7%*
Heart	Absolute wt.	+0.7%	+14.3%	NC	+7.4%	+11.7%	+9.6%
	Relative-to body weight	-1.2%	+5%	+3.8%	+1.3%	+5%	+4.7%
	Relative-to-brain weight	-0.8%	+10%*	-0.4%	+2%	+6.4%	+9.5%
Liver	Absolute wt.	+8.9%*	+25.5%*	+17.9%*	+13.8%*	+28.4%*	+49.7%*
	Relative-to body weight	+6.6%	+14.6%	+21.4%*	+8.5%	+22.2%*	+44.3%*
	Relative-to-brain weight	+7.1%	+20.5%*	+16.6%*	+8.8%	+23.2%	+50.6%*
Pituitary	Absolute wt.	NC	+7.1%	NC	+6.3%	+12.5%*	+12.5%*
	Relative-to body weight	NC	NC	+2.9%	+1.6%	+7.8%	+10.9%
	Relative-to-brain weight	+2.7%	+5.5%	-1.4%	+3.3%	+10%	+77.8%*

*: Significant different from control value, $p \leq 0.05$ NC: No changes

Histopathology: No treatment-related microscopic effects were observed. However histological examination of the high-dose female liver revealed treatment-related microscopic changes. Light microscopy revealed minimal to moderate hypertrophy of hepatocytes. Electron microscopy revealed hypertrophy of hepatocytes Also, centrilobular and peripheral hepatocytes showed a mild to morphological changes in the hepatocytes, moderate hypertrophy with increased rough endoplasmic reticulum and a mild proliferation of mitochondria. These changes can be correlated to the observed increase in alanine aminotransaminase and alkaline phosphatase.

Study title: 6-Month Chronic Toxicity Study of SPM 927 by Oral Administration to Sprague-Dawley Rats.

Key study findings: SPM 927 (0, 30, 90, and 180 mg/kg/day) was administered orally to rats for 6 months with the following results:

1. Absorption was rapid; T_{max} was between 0.5 and 2 hours.
2. AUC and C_{max} increased in a dose-dependent fashion; however, the increase was less than dose proportional.
3. One treatment-related mortality was observed. A male in the high dose (180 mg/kg/day) group died. However, no macroscopic findings were identified.
4. Treatment-related signs of toxicity were only observed in the high-dose (180 mg/kg/day) group. The primary clinical signs included excessive salivation,

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reduced motility and apathy. The onset of the clinical signs were rapid and persisted for hours; starting 15 to 20 minutes after dosing and lasted a few hours (reduced motility) or up to 24 hours (salivation). Reduced motility and apathy peaked within the range of T_{max} for lacosamide.

5. There were no drug-related gross and histological findings.
6. At 180 mg/kg/day, ALT levels were increased. Relative to control, ALAT were significantly increased by 43% at week 13 in females. Although not statistically significant, ALT was increased by 30% in the high dose females. ALAT level in high dosed males was increased (not statistically significant) by 22% and 9.5% at week 13 and 26, respectively.
7. In females at 180 mg/kg, compared to the controls, relative liver weights and liver-to-brain weight ratio were increased by 13.3% and 14.8%, respectively. The increased relative liver weight and liver-to-brain weight ratio was reversible; they were within normal range after a 4-week recovery period.
8. Diuretic-like effect was observed in the high dose females. The urine volume was increased by 12% and 84% at 180 mg/kg in males and females, respectively. Also, water consumption was increased in the females in the high dose group. Compared to the controls, water consumption was transiently increased up to 21% in week 6. Specific gravity was minimally, but statistically significantly, decreased in females at 90 and 180 mg/kg.
9. The NOAEL was 90 mg/kg/day; this dose is associated with an AUC_{0-24} of 325.8 h.µg/mL and C_{max} of 27.45 µg/mL.

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Study no.: — **Report № 13227/00**
Volume #, and page #: Electronic document
Conducting laboratory and location: —

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Date of study initiation: June 8, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № KK 02457, 99.71%

Methods

Doses: 0, 30, 90, and 180 mg/kg/day
Species/strain: Sprague-Dawley Rats / — CD®BR
Number/sex/group or time point (main study):

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Group	Test Article	Dosage Level (mg/kg/day)	Dosage Volume (mL/kg)	Number of Animals	
				Females	Males
Main					
1	SPM 927	0	5.0	20	20
2	SPM 927	30	5.0	20	20
3	SPM 927	90	5.0	20	20
4	SPM 927	180	5.0	20	20
Recovery					
1	SPM 927	0	5.0	5	5
2	SPM 927	30	5.0	5	5
3	SPM 927	90	5.0	5	5
4	SPM 927	180	5.0	5	5
Satellite					
2	SPM 927	30	5.0	20	20
3	SPM 927	90	5.0	20	20
4	SPM 927	180	5.0	20	20

Route, formulation, volume, and infusion rate: Oral (gavage), Solution, 5.0 mL/kg
Satellite groups used for toxicokinetics or recovery: Yes: Groups included for toxicokinetics (10/sex/dose group) and recovery (5/sex/group)
Age: Males: 26 days; Females: 28 days
Weight: Males: 89.4-100.9 g; Females: 89.5-100.8 g
Sampling times: See below.
Unique study design or methodology (if any):

Observations and times:
Toxicokinetics: Blood samples were collected from satellite animals in groups 2 to 4. Blood was drawn on test day 1and during weeks 13, and 26 for toxicokinetic evaluation at 0.5, 1, 2, 4, 8, and 24 hours after dosing. Each satellite animal was used at two time-points according to the table below (replicated from Sponsor's submission).

Sampling Time after dosing on test day and in test weeks 13 and 26	Sampling from animal №			№ of Plasma Samples
	Group 2	Group 3	Group 4	
0.5 and 4 hr	M: 201-203 F: 211-213	M: 221-223 F: 231-233	M: 241-243 F: 251-253	108
1 and 8 hr	M: 204-206 F: 214-216	M: 224-226 F: 234-236	M: 244-246 F: 254-256	108
2 and 24 hr	M: 207-209 F: 217-219	M: 227-229 F: 237-239	M: 247-249 F: 257-259	108

Mortality: Mortality was examined twice daily (early morning and afternoon), except on weekends the second check was conducted at mid-day.
Clinical signs: During the first two weeks of the study, each animal was examined daily for treatment-related clinical signs. Thereafter, the animals were examined weekly. The

animals were examined approximately 0.5 hours after dosing for any signs or reaction to the treatment. When clinical signs were observed, the animal(s) was observed at hourly intervals until the symptoms disappeared. In addition to these observation periods, the animals were checked regularly throughout the working day from 7:00 am to 4:30 pm.
Body weights: Body weights were recorded at randomization, prior to treatment and weekly thereafter.
Food consumption: Food consumption was recorded weekly. In addition, water consumption was measured in animals (10/group/sex) scheduled for the urinalysis for 7 days in weeks 6, 13, and 25.
Ophthalmoscopy: Eyes of all animals were examined before the first dose and during test weeks 13 (TD 92), and 26 (TD 182) as well at the end of the 4-week recovery period (TD 206). During the examination of the eye, the following ocular structures were examined: adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus. Also auditory acuity was evaluated in all surviving animals after 26 weeks of treatment (TD 182) and at the end of the recovery period (TD 206).
EKG: Not performed
Hematology: Blood was collected from animals (first 10 surviving/sex/group) in the main study during weeks 13 (TD 87) and 26 (TD 178). Blood was collected from the recovery animals during test week 30 (TD 206). The following parameters were examined: hemoglobin (HGB), erythrocytes, leucocytes, hematocrit % (HCT%), platelet count (PLT), reticulocytes (RET; % of the erythrocytes), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), thromboplastin time, activated partial thromboplastin time (APT), differential blood cell count, and blood cell morphology.
Clinical chemistry: The following parameters were measured from animals (first 10 surviving/sex/group) in the main study during weeks 13 (TD 87) and 26 (TD 178); and the recovery animals during test week 30 (TD 206): sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphate (PHOS), urea (UN), glucose (GLU), tricyclerides, total cholesterol (CHOL), creatinine (CREA), total protein (TP), albumin (ALB), globulin (GLOB), total bilirubin, albumin/globulin ratio (AGR), alkaline phosphatase (ALP), aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), and lactate dehydrogenase (LDH).
Urinalysis: Urine was collected from overnight fasted main study animals (10/sex/group) during weeks 13 (TD 87) and 26 (TD 178). Urine was collected from the recovery animals during week 30 (TD 206). Urine was collected for 16 hours prior to collecting blood for hematological and clinical chemistry evaluations. The following parameters were evaluated: total volume, specific gravity, pH, bilirubin, hemoglobin, nitrite, protein, ketones, glucose, and urobilinogen. Microscopically the urine was examined for deposits of: epithelial cells, leucocytes, erythrocytes, organisms, crystalluria and other constituents (i.e., sperms and casts).
Gross pathology: Surviving animals were anesthetized with ether on test day 183 (24 hours after last dosing) or test 184 (24 hours after last dosing) exsanguinated. Macroscopic evaluation was performed on all orfices, external surface of the body, cranial cavity, external surfaces of the brain, pituitary gland, and cranial nerves, organs, thoracic viscera (special attention to the thymus, lymph nodes and heart), abdominal, and pelvic cavities and viscera. The liver and kidney were also examined externally.

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Organ weights: The weight of the following organs was measured at necropsy in all animals: adrenal (2), brain, epididymis (2), heart, kidney (2), liver, lungs, ovary (2), pituitary, prostate, seminal vesicle, spleen, testicle (2), thyroids/parathyroids (1), and uterus. The adrenals, gonads and kidneys were weighed individually and identified as right or left.

Histopathology: The following tissues were collected from all animals at necropsy and those that died during the study:

Dose (mg/kg)	0	30	90	180
Species	Rat			
Adrenals	X	X	X	X
Aorta abdominalis	X	X	X	X
Bone Marrow smear (femur)	X	X	X	X
Bone (femur with joint)	X	X	X	X
Brain (cerebrum, cerebellum, brain stem)	X	X	X	X
Cecum	X	X	X	X
Cervix	X	X	X	X
Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis (2)	X	X	X	X
Esophagus	X	X	X	X
Eye	X	X	X	X
Fallopian tube				
Gall bladder				
Gross lesions (incl. surrounding lymph nodes)	X	X	X	X
Harderian gland	X	X	X	X
Heart (left & right ventricles, septum)	X	X	X	X
Ileum	X	X	X	X
Injection site				
Jejunum	X	X	X	X
Kidneys and ureter (2)	X	X	X	X
Lachrymal gland				
Larynx	X	X	X	X
Liver	X	X	X	X
Lungs with mainstem bronchi & bronchioles	X	X	X	X
Lymph nodes, cervical	X	X	X	X
Lymph nodes mandibular	X	X	X	X
Lymph nodes, mesenteric	X	X	X	X
Mammary Gland	X	X	X	X
Nasal cavity				
Optic nerves	X	X	X	X
Ovaries (2)	X	X	X	X

Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve				
Pharynx*	X	X	X	X
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum	X	X	X	X
Salivary gland (mandibular, sublingual, parotid gland)	X	X	X	X
Sciatic nerve	X	X	X	X
Seminal vesicles	X	X	X	X
Skeletal muscle (leg)	X	X	X	X
Skin	X	X	X	X
Spinal cord (3 sections)	X	X	X	X
Spleen	X	X	X	X
Sternum (with marrow)	X	X	X	X
Stomach	X	X	X	X
Teeth (2 incisors, 2 molars)*	X	X	X	X
Testes (2)	X	X	X	X
Thymus	X	X	X	X
Thyroid (2)	X	X	X	X
Tongue (incl. Base)	X	X	X	X
Trachea	X	X	X	X
Urinary bladder	X	X	X	X
Uterus (incl. Oviducts)	X	X	X	X
Vagina	X	X	X	X
Zymbal gland				

Tissues were fixed in 7% neutral-buffered formalin. All tissues, with the exception of those marked with an asterisk, with hematoxylin and eosin stain and examined histologically from animals in groups 1 and 4. Also, frozen sections of the heart, liver, and kidney were made and stained with scarlet R and examined histologically for the presence of triglycerides in all animals in groups 1 and 4.

Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )

Results

Toxicokinetics: A summary of the toxicokinetic values at each of the doses examined are presented in table 1 below.

Table 1. Comparison of Toxicokinetic parameters

Drug Day	TK Parameter	SPM 927 (mg/kg)								
		30			90			180		
		M[a]	F[a]	F+M[b]	M[a]	F[a]	F+M[b]	M[a]	F[a]	F+M[b]

1	Cmax (µg/mL)	12.91	14.03	13.93 ± 0.99	23.58	25.27	24.42 ± 3.64	32.71	30.67	32.30 ± 4.05
	AUC_{0-24h} (h.µg/mL)	105.7	118.9	113.1 ± 12.5	261.5	311.0	277.1 ± 37.3	400.1	480.9	459.2 ± 60.5
	Tmax (h)	1.0	1.0	1.3 ± 0.6	1.0	2.0	1.3 ± 0.8	1.0	0.5	1.0 ± 0.5
91	Cmax (µg/mL)	11.62	13.72	12.47 ± 1.35	27.85	26.41	27.17 ± 1.62	38.17	33.93	38.46 ± 7.83
	AUC_{0-24h} (h.µg/mL)	120.5	133.7	127.9 ± 29.3	275.3	310.0	268.5 ± 50.1	539.0	500.7	511.2 ± 121.5
	Tmax (h)	2.0	0.5	1.8 ± 1.3	0.5	1.0	1.2 ± 0.7	2.0	1.0	2.8 ± 2.9
182	Cmax (µg/mL)	11.23	12.35	12.26 ± 1.48	21.76	33.71	27.45 ± 6.98	47.01	62.38	53.55 ± 9.85
	AUC_{0-24h} (h.µg/mL)	139.7	130.6	136.7 ± 18.1	296.1	339.0	325.8 ± 58.7	488.4	569.8	543.5 ± 87.3
	Tmax (h)	1.0	1.0	1.0 ± 0.5	4.0	1.0	2.5 ± 3.0	0.5	1.0	0.8 ± 0.3

a: All values are given as median
b: All values are given as mean

Lacosamide (SPM 927) was rapidly absorbed at all doses with mean maximum plasma concentrations reached between 0.5 and 2 hours for each dose tested at days 1 and 91.

The mean C_{max} and AUC_{0-24} values increased with dose but in a less than dose-proportional manner. A less than proportional increase in AUC_{0-24} exposure suggests saturation of the absorption and elimination processes at higher doses. In fact, a 6-fold increase in dose (30-180 mg/kg/day) resulted in a 4.0-fold increase in AUC_{0-24} on days 1 and 182. After repeated dosing for 6 months, the 24-hour exposure was up to 1.2-fold higher as compared to day 1. On day 182, a 4.4-fold increase in AUC_{0-24} and C_{max} was noted.

Mortality: No treatment-related deaths were noted in males in the 30 and 90 mg/kg treatment groups or females in the 90 and 182 mg/kg treatment groups; all animals survived to the scheduled study termination. One male in the high-dose group (182 mg/kg) died on day 147; no macroscopic findings were noted at necropsy. The Sponsor considered this death to be treatment-related. One female in the low-dose group was found dead on day 163; macroscopic findings were noted in the lymph node, thymus, salivary gland and abdominal cavity. The Sponsor concluded that this death was not treatment-related.

Dose (mg/kg)	Animal № (sex)	Day of Death	Comments	Macroscopic Finding
0	29 (Female)	178	Died during blood withdrawal procedure. Death related to the ether anaesthesia.	No pathological findings
30	85 (Female)	163	- Found dead in the morning - Sponsor considered the death to be spontaneous and associated with the tumor-like enlargement	**Lymph Node (mesenteric):** Severely enlarged **Caecum:** Hemorrhagic focus (approx. 0.5 cm) **Thymus:** Severly enlarged and indurated (2.5 x 2 x 2 cm; 7. 24 g)

			in the region of the thymus and liver.	**Lungs:** caudal part adhere to pericardium **Tissue Enlargement:** located in abdominal cavity caudal of liver, of fat-tissue-like consistency, partly indurated, white-grey discoloured (2.5 x 1.5 x 0.5 cm) **Salivary Gland:** thickened and enlarged
180	171 (Male)	147	- Found dead in the morning. - Treatment-related.	No macroscopic changes identified.

Clinical signs: The Sponsor did not provide individual animal data for clinical signs of toxicity. However, a summary of the findings was provided from which the table below was constructed by the reviewer. Table 2 summarizes the clinical signs of toxicity observed and on the days on which the observation started.

Salivation, reduced motility, and apathy were the primary drug-induced toxicity. Starting at day 15 (week 2) through day 49 (week 7), salivation was observed in all males in the 180 mg/kg/day treatment group. During weeks 8 through week 20, individual animals presented with increased salivation. According to the Sponsor the increased salivation lasted for 24-hours. The Sponsor graded the increased salivation as moderate.
All animals displayed reduced motility starting on day 24 and persisted to the end of the study. The intensity of the reduced motility increased with increasing exposure to the test drug. The Sponsor scored the severity of the reduced motility as mild, moderate-marked, and severe during weeks 4-9, weeks 10-15, and week 16 onward, respectively.
Apathy was observed from day 99 to the end of study on day 182. The Sponsor rated the apathy as moderate. Abdominal or lateral position and increased muscle tones were other treatment-related clinical signs noted. According to the Sponsor, the intensity of these overt clinical signs was mild.

Table 2. Summary of lacosamide-induced clinical signs.

Clinical Sign	Dose (mg/kg)	Observation
		Males (n = 25)
	0	No clinical signs noted
	30	No drug-induced toxicity
	90	No treatment-induced toxicity.
Increased Salivation	180	Day Toxicity Started: Day 15 Severity Score: Moderate Days 15 – 49: All animals (n = 25) Day 50 - 137: seen in individual animals (1 –4 animals)
Reduced Motility		Day Toxicity Started: Day 24 Days 24 – 182All Animals (n = 25; n = 24 after D146) Severity Score: Mild (D24-D70); Mild-Moderate (D71-D77); Moderate (D78-D91); Moderate-Severe (D92-D105); Severe (D106-D182)
Apathy		Day Toxicity Started: Day 99 Days 99-182: All animals (n = 25)
Abdominal position		Day Toxicity Started: Day 64 Days 64-127-observed in individual animals (1-2) on some of the days during this period
Lateral Position		Day Toxicity Started: Day 73 Days 73-133: observed in individual animals (n = 1) on some days during this

		period
Increased muscle tone		Day Toxicity Started: Day 24 Days 24-31: All animals (n = 25); Mild severity
		Females (n=25)
	0	No clinical signs noted
	30	No mortality No treatment-related clinical signs
	90	No mortality No treatment-related clinical signs
Increased Salivation	180	Day Toxicity Started: Day 10 Severity Score: Moderate Days 10-49: All animals (n = 25) Day 50 - 137: seen in individual animals (1 –6 animals)
Reduced Motility		Day Toxicity Started: Day 24 Days 24-182 : All Animals Severity Score: Mild (D24-D70); Mild-Moderate (D71-D77); Moderate (D78-D91); Moderate-Severe (D92-D105); Severe (D106-D182)
Apathy		Day Toxicity Started: Day 99 Days 99-182: All animals
Abdominal position		Day Toxicity Started: Day 64 Days 64-136-observed in individual animals (1-3) on some of the days during this period
Lateral position		Day Toxicity Started: Day 69 Days 69-154: observed in individual animals (n = 1-2) on some days during this period
Increased muscle tone		Day Toxicity Started: Day 24 Days 24-32: All animals (n = 25); Mild severity

Body weights: There were no statistically significant differences in group mean body weights in females treated with lacosamide compared to vehicle treated animals.

Relative to control, males treated with lacosamide showed decreased mean group body weight in the mid- and high-dose groups. Males treated with 90 mg/kg/day had significant decrease (6%) group mean body weights in week 19 compared control males. Mean body weight of males treated with 180 mg/kg/day was decreased 6% to 7% during weeks 18-22, 24 and 26. The following summary tables shows significant effects in body weight treatment-related changes in males:

Table Summary of significant changes in mean body weight compared to control

		Dose (mg/kg/day) ± SD			
Week	**Sex**	**0**	**30**	**90**	**180**
18	M	535.2 ± 37.2	529.6 ± 44.1 (-1%)	509.4 ± 42.3 (-5%)	504.5 ± 43.6 (-6%)*
19	M	546.5 ± 39.8	536.28 ± 43.0 (11.8%)	515.4 ± 43.7 (-6%)*	508.9 ± 41.1 (-7%)*
20	M	552.0 ± 41.4	542.3 ± 44.5 (-2%)	523.0 ± 43.5 (-5%)	513.6 ± 42.1 (-7%)*
21	M	560.7 ± 38.8	552.4 ± 49.5 (-2%)	528.9 ± 43.1 (-6%)	520.5 ± 45.5 (-7%)*
22	M	563.5 ± 39.5	554.7 ± 50.7 (-2%)	535.8 ± 43.4 (-5%)	523.5 ± 44.7 (-7%)*
24	M	562.8 ± 37.4	559.7 ± 47.2	539.2 ± 41.1	529.5 ± 43.4

			(-0.6%)	(-4%)	(-6%)*
26	M	585.8 ± 39.2	571.5 ± 56.0 (-2%)	555.3 ± 47.1 (-5%)	544.9 ± 45.7 (-7%)*

*: Statistically significant (at p≤0.01) differences in mean body weight compared to controls

Food consumption: All rats had comparable food intake at beginning of dosing. Food consumption in the male was not affected by lacosamide treatment but compared to controls, a dose responsive reduction in food consumption was observed in females at the 90 and 180 mg/kg dose. Females treated with 90 mg/kg/day food intake was significantly reduced by 10.8%, 10.4%, 7.8%, and 11.0% at weeks 1, 4, 4 and 23 respectively. Females treated with180 mg/kg/day showed decreased food intake in by 9.1% to 20% during weeks 1 thru 10, weeks 16 and 23. Significant changes in food consumption are tabulated below.

Summary of significant changes in mean food consumption compared to control

Weekly Mean Food Consumption (g/kg/day) ± SD					
		Dose (mg/kg/day)			
Week	**Sex**	**0**	**30**	**90**	**180**
0	F	122.9 ± 21.2	116.3 ± 10.2	118.0 ± 11.1	114.9 ± 12.9
1	F	117.5 ± 22.0	112.7 ± 11.6 (-4.1%)	104.8 ± 10.1 (-10.8%)*	93.6 ± 12.0 (-20%)*
2	F	111.0 ± 20.0	108.6 ± 15.7 (-2%)	103.9 ± 19.3 (-6.4%)	95.8 ± 12.6 (-13.7%)*
3	F	109.7 ± 22.7	110.1 ± 20.4 (+1%)	104.1 ± 28.0 (-5.1%)	92.7 ± 9.5 (-15.5%)*
4	F	105.3 ± 18.6	98.0 ± 15.5 (-6.9%)	94.4 ± 18.0 (-10.4%)*	85.8 ± 10.3 (-18.5%)*
5	F	96.6 ± 11.8	92.9 ± 11.9 (-3.8%)	88.9 ± 13.0 (-7.8%)*	84.6 ± 8.8 (-12.4%)*
6	F	93.1 ± 14.5	88.9 ± 14.9 (-4.5%)	88.7 ± 15.4 (-4.7)	82.2 ± 12.2 (-11.7%)*
7	F	87.0 ± 14.1	82.3 ± 11.4 (-5.4%)	82.8 ± 14.1 (-4.8%)	76.4 ± 9.9 (-12%)*
8	F	85.9 ± 14.4	83.8 ± 11.1 (-2.4%)	83.4 ± 14.5 (-2.9%)	75.4 ± 8.1 (-12.2)*
9	F	83.0 ± 14.7	79.2 ± 12.0 (-4.6%)	79.6 ± 13.2 (-4.1%)	74.2 ± 8.1 (-10.6%)*
10	F	82.6 ± 13.1	80.7 ± 13.0 (-2.3)	77.9 ± 12.8 (-5.7%)	73.0 ± 9.5 (11.6%)*
16	F	70.4 ± 10.9	71.4 ± 14.1 +1.4%)(	66.0 ± 7.4 (-6.3%)	62.2 ± 6.6 (-11.6%)*
23	F	66.8 ± 9.9	64.2 ± 8.6 (-3.9%)	59.4 ± 6.7 (-11%)*	60.7 ± 5.2 (-9.1%)*

*: Statistically significant (at p≤0.01) differences in mean food consumption compared to controls

Ophthalmoscopy: No treatment-related changes were noted in the eye.

EKG: Not assessed

Hematology: No statistically significant or biologically significant differences in hematology chemistry values were observed between lacosamide treated female rats in the low-, mid- and high-dose groups and the vehicle treated rats.

Mean MCHC value (338.79 ± 7.52) for males treated with 180 mg/kg/day of lacosamide was increased by 3% during week 13 compared to the values for control males (328.48 ± 7.39). The mean MCHC value returned to control levels after the 4-week recovery period. No other hematological changes were noted in males.

Clinical chemistry: No statistically significant changes were observed in the clinical chemistry parameters between the lacosamide treated animals in the low- and mid-dose groups and the vehicle treated animals.

Statistically significant differences from controls occurred in the 180 mg/kg/day group. Differences are listed in accompany table. Females treated with 180 mg/kg of lacosamide showed a statistical significant ($p \leq 0.01$) increase in total cholesterol plasma values compared to control. Females mean total cholesterol values were increased 41% and 25% at weeks 13 and 26, respectively; but returned to control levels after the 4-week recovery period. Although not statistically significant, total serum cholesterol was increased males in the high dose group; mean values were increased 29% and 20% at weeks 13 and 26, respectively.

Changes in ALAT levels were observed. The high-dose of lacosamide increased ALAT activity. Male ALAT values were increased 22% and 9.5% at weeks 13 and 26, respectively. Changes in females ALAT levels at week 13 were statistically significant. Female ALAT values were increased 43% and 30% at weeks 13 and 26, respectively; but returned to control levels after recovery. The increase in the mean ALAT level was the result of individual animals having an increase level and did not demonstrate a dose-dependent pattern. Therefore, this finding is of little toxicological significance. No other statistically significant changes in clinical chemistry parameters were observed in females.

Parameter	Drug Week	Sex	Dose (mg/kg)	
			0	180
Cholesterol (Total)	13	M	1.592 ± 0.384	2.058 ± 0.161 (+29%)
		F	1.977 ± 0.445	2.792 ± 0.520 (+41%)*
	26	M	1.916 ± 0.340	2.298 ± 0.280 (+20%)
		F	2.452 ± 0.593	3.057 ± 0.518 (25%)*
ALAT (GPT)	13	M	43.4 ± 6.4	52.8 ± 12.8 (+22%)
		F	35.3 ± 5.9	50.5 ± 13.0 (+43%)*
	26	M	57.7 ± 11.0	63.2 ± 7.7 (+9.5%)
		F	50.9 ± 9.5	66.3 ± 15.9

b(4)

				(+30%)

*: Statistically significant (at p≤0.01) differences compared to controls

Urinalysis: No treatment-related alterations in urinalysis parameters were observed with analysis of urine or urine sediment. However, lacosamide-related effects on urine volume and specific gravity were observed and are tabulated below.

Parameter	Drug Week	Sex	Dose (mg/kg)		
			0	90	180
Specific Gravity (g/mL)	13	M	1.038 ± 0.008	1.036 ± 0.006	1.037 ± 0.010
		F	1.038 ± 0.008	1.044 ± 0.014	1.038 ± 0.012
	26	M	1.036 ± 0.007	1.046 ± 0.014	1.034 ± 0.007
		F	1.058 ± 0.011	1.041 ± 0.013 (-1.6%)*	1.040 ± 0.015 (-1.7%)*
Urine Volume (mL/kg/24 hr)	13	M	25.0 ± 7.9	28.8 ± 6.1 (+15.2%)	31.0 ± 7.8 (+24%)
		F	29.3 ± 7.9	31.7 ± 14.1 (+43%)	38.6 ± 15.8 (+31.7%)
	26	M	23.3 ± 6.5	20.5 ± 6.7 (-12.01%)	26.1 ± 5.8 (+12.01%)
		F	15.6 ± 5.7	22.8 ± 9.9 (+46.2%)	29.2 ± 13.7 (+87.2%)

*: Statistically significant (at p≤0.01) differences compared to controls

Slight but significant decreased urinary specific gravity was observed in female rats treated with 90 or 180 mg/kg/day. The Sponsor considered this to be spontaneous and not lacosamide-related. Urine volume was increased (not significant at $p \leq 0.01$) at 180 mg/kg/day in both males and females. Compared to the controls, urine volume was increased by 24% (week 13) and 12% (week 26) for the males and by 32% (week 13) and 87 (week 26) for the females.

Gross pathology: No drug-related changes were observed.

Organ weights: At the end of the 26 week study period, the group mean relative organ weight and organ-to-brain weight ratio compared to the control was significantly (at p≤0.01) increased in the high-dose females for the liver by 13.3% and 14.8%, respectively; but returned to control levels after the 4-week recovery period. No statistically significant changes were observed in relative or absolute group mean organ weights in males or females at any doses.

Histopathology: No drug-related changes were observed in lacosamide treated animals compared to control.

Study title: 12-Month Chronic Toxicity Study of SPM 927 by Oral Administration to Beagle Dogs.

Key study findings: Lacosamide (0.0, 5.0, 10.0, and 20/25 mg/kg/day) was administered orally to dogs for 12 months with the following results:

1. Absorption was fairly rapid (T_{max} was between 1.0 and 2 hours). AUC and C_{max} were dose-dependent; exposure increased with increasing doses. However, the increase was less than dose proportional when the dose was increased from 5.0 mg/kg/day to 20/25 mg/kg/day.
2. No animals died due to drug treatment prior to schedule sacrifice.
3. No treatment-related clinical signs were noted in the 5.0 and 10.0 mg/kg/day treatment groups.
4. Tonic-clonic convulsions were the primary treatment-related toxicity associated with the 25 mg/kg/day dose of lacosamide. Other treatment-related overt signs of toxicity noted following the 25 mg/kg/day dose were ataxia, reduced motility, tremor and increased salivation.
5. No treatment-related macroscopic or histological changes were noted.
6. Heart rate of the lacosamide treated males and females in the mid- and high-dose groups were slightly higher that that of the control 2 hours after dosing on weeks 13, 26, 39, and 52. The difference from the control was between plus 2% to 36% (not statistically significant).
7. Treatment-related effects on peripheral arterial blood pressure were observed in both males and females. Blood pressure was decreased in males in the 5 mg/kg/day group and females in the 10 and 20/25 mg/kg/day group.
8. The NOAEL was 10 mg/kg/day (in agreement with the Sponsor; HED = 5.4 mg/kg) based on the lack of toxicological findings and based on the increased heart rate not being statistically significant and is monitorable. This corresponds to AUC values of 71.0 and 54.6 h.µg/mL in males and females respectively, after repeated daily dosing for 12 months. C_{max} values at this dose were 15.52 and 13.15 µg/mL in males and females, respectively.

b(4)

Study no.: — **Report № 13196/00**
Volume #, and page #: Electronic document
Conducting laboratory and location: —— b(4)

Date of study initiation: May 29, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 927, Batch № WE 11174, 99.72%

Methods

Doses: 0, 5, 10, 20 (wk 1 to end of wk 5), and 25 (wk 6 to end of study) mg/kg
Species/strain: Dog/Beagle
Number/sex/group or time point (main study):

Group	Test Article	Dosage Level (mg/kg/day)	Number of Animals	
			Females	Males
Main Study				
1	SPM 927	0	5	5
2	SPM 927	5	5	5
3	SPM 927	10	5	5
4	SPM 927	Wk 1 to end of wk 5: 20 Wk 6 to end of study: 25	5	5
TK Study				
6	SPM 927	0	2	2
7	SPM 927	5	2	2
8	SPM 927	10	2	2
9	SPM 927	Wk 1 to end of wk 5: 20 Wk 6 to end of study: 25	2	2

Route, formulation, volume, and infusion rate: Oral, gelatine capsule
Satellite groups used for toxicokinetics or recovery: 2/sex/group
Age: 5.5 months
Weight: Males: 6.0 – 8.5 kg; Females: 4.8 – 6.3 kg
Sampling times: See below.
Unique study design or methodology (if any): None.

Toxicokinetics: Blood samples were collected from all recovery animals in groups 2 to 4. Blood was drawn during weeks 1, 13, 39 and 52 for toxicokinetic evaluation at 0.5, 1, 2, 4, 8, and 24 hours after dosing.
Mortality: Mortality was examined twice daily (morning and afternoon).
Clinical signs: Each animal was examined before and after each dosing for treatment-related clinical signs. The animals were examined approximately 0.5 hours after dosing for any signs or reaction to the treatment. Each clinical signs were observed, the animal(s) was observed until the symptoms disappeared. In addition to these observation periods, the animals were checked regularly throughout the working day from 7:00 and to 4:00 pm.
Body weights: Body weights were recorded at study initiation, and weekly thereafter on the same weekday.
Food consumption: Food consumption was recorded daily.
Ophthalmoscopy: Eyes of all animals were examined before the first dose and at the end of test weeks 13, 26, 39 and 52 as well at the end of the 4-week recovery period. During the examination of the eye, the following ocular structures were examined: adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus.

EKG: Electrocardiography recordings were performed before and 2 hours after dosing on test days 1 and 3, at end of weeks 13, 26, 39, and 52. EKG was also performed on the

recovery animals at the end of week 56. The standard bipolar limb leads (I, II and III), augmented leads aVR, aVL and aVF were recorded.

Blood Pressure: Blood pressure (BP) was measured before and 2 hours 5 min after dosing on at the end of weeks 13, 26, 39, and 52. BP was also measured in the recovery animals at the end of week 56.

Hematology: Blood was collected prior to first dosing, at the end weeks 13 and 26 (TD 89/90, 180/181) and at the end of weeks 39 and 52 (TD 271/272, TD 362/363). Blood was also collected from the recovery animals at the end of test week 56. The following parameters were examined: hemoglobin (HGB), erythrocytes, leucocytes, hematocrit % (HCT%), platelet count (PLT), reticulocytes (RET; % of the erythrocytes), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), activated partial thromboplastin time (aPTT), thromboplastin time, erythrocyte sedimentation rate (ESR), differential blood cell count, and blood cell morphology

Clinical chemistry: Blood was collected prior to first dosing, at the end weeks 13 and 26 (TD 89/90, 180/181) and at the end of weeks 39 and 52 (TD 271/272, TD 362/363). In addition, blood was also collected from the recovery animals at the end of test week 56. The following parameters were measured: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphate, urea in blood (BUN), glucose (GLU), total cholesterol (CHOL), creatinine (CREA), total protein (TP), albumin (ALB), globulin (GLOB), bile acid, albumin/globulin ratio (AGR), alkaline phosphatase (AP), aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), gamma glutamyl-transferase (γ-GT), tricyclerides, lactate dehydrogenase (LDH), and total bilirubin (TBIL).

Urinalysis: Urine was collected prior to the first of dosing, at the end of weeks 13 and 26 (TD 89/90, 180/181) and at the end of weeks 39 and 52 (TD 271/272, TD 362/363). Urine was collected from the recovery animals at the end of test week 56. The following parameters were evaluated: total volume, specific gravity, pH, bilirubin, hemoglobin, nitrite, protein, ketones, glucose, and urobilinogen. Microscopically the urine was examined for deposits of: epithelial cells, leucocytes, erythrocytes, organisms, crystalluria and other constituents (i.e., sperms and casts).

Gross pathology: Surviving animals were anesthetized with T61, and exsanguinated. Macroscopic evaluation was performed on all orifices, external surface of the body, cranial cavity, external surfaces of the brain pituitary gland, and cranial nerves, organs, thoracic (special attention to the thymus, lymph nodes and heart), abdominal, and pelvic cavities and viscera.

Organ weights: The weight of the following organs was measured at necropsy in all animals: adrenal (2), brain, epididymis (2), heart, kidney (2), liver, lungs, ovary (2), pituitary, prostate, spleen, testicle (2), thyroids/parathyroids (2), and uterus.

Histopathology: The following tissues were collected from all animals at necropsy:

Dose (mg/kg)	0	5	10	20/25
Species	Dogs			
Adrenals	X	X	X	X
Aorta abdominalis	X	X	X	X
Bone Marrow smear (femur)	X	X	X	X
Bone (femur)	X	X	X	X
Brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular part)	X	X	X	X
Cecum	X	X	X	X
Cervix	X	X	X	X
Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis (2)	X	X	X	X
Esophagus	X	X	X	X
Eye (2)	X	X	X	X
Fallopian tube	X	X	X	X
Gall bladder	X	X	X	X
Gross lesions	X	X	X	X
Harderian gland				
Heart (left & right ventricles, septum)	X	X	X	X
Ileum	X	X	X	X
Injection site				
Jejunum	X	X	X	X
Kidneys (and ureter)	X	X	X	X
Lachrymal gland (2)	X	X	X	X
Larynx	X	X	X	X
Liver	X	X	X	X
Lungs (with mainstem bronchi & bronchioles)	X	X	X	X
Lymph nodes, cervical	X	X	X	X
Lymph nodes mandibular	X	X	X	X
Lymph nodes, mesenteric	X	X	X	X
Mammary Gland	X	X	X	X
Muscle (skeletal)	X	X	X	X
Nasal cavity				
Optic nerves (2)	X	X	X	X
Ovaries	X	X	X	X
Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve				
Pharynx*	X	X	X	X
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum	X	X	X	X

Salivary gland (mandibular, sublingual & parotid gland)	X	X	X	X
Sciatic nerve	X	X	X	X
Seminal duct*	X	X	X	X
Seminal vesicles (2)	X	X	X	X
Skeletal muscle (thigh)	X	X	X	X
Skin (left flank)	X	X	X	X
Spinal cord (3 sections)	X	X	X	X
Spleen	X	X	X	X
Sternum				
Stomach	X	X	X	X
Tattoo*				
Teeth (2 incisors, 2 molars)*				
Testes (2)	X	X	X	X
Thymus	X	X	X	X
Thyroid (2) with parathyroid	X	X	X	X
Tissue masses or tumors (incl. Regional lymph nodes)	X	X	X	X
Tongue (incl. Base)	X	X	X	X
Trachea	X	X	X	X
Urinary bladder	X	X	X	X
Uterus	X	X	X	X
Vagina	X	X	X	X
Zymbal gland				

Tissues were fixed in 10% neutral-buffered formalin. All tissues, with the exception of those marked with an asterisk, with hematoxylin and eosin stain and examined histologically. Also, frozen sections of the heart, liver, and kidney were made and stained with scarlet R and examined histologically for the presence of triglycerides.

Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Other: Using a simple noise test, auditory acuity was checked predosing and at the end of weeks 13, 26, 39, 52 and 56 (end of recovery period) using a simple noise test.

Results

Toxicokinetics: Blood samples were collected from the main study animals on treatment weeks 1, 13, 39, and 52 at 0.5, 1, 2, 4, 8, and 24 hours after dosing. Also blood samples were collected from all recovery animals in groups 2 to 4.

As indicated in the table below, following the first oral dose of lacosamide, absorption was rapid, mean peak plasma concentrations were achieved within 1 hour. Mean peak

plasma concentrations on day 1 were 6.73, 11.05 and 20.12 µg/mL following 5, 10 and 20/25 mg/kg/day. The mean $AUC_{(0\text{-}24h)}$ values were 1.89, 39.6 and 82.1 following 5, 10 and 20/25 mg/kg/day. The median lacosamide plasma concentrations at all dose levels on day 1 or in week 52 indicate a slightly higher exposure in males than in females.

Systemic exposure as defined by the C_{max} and $AUC_{(0\text{-}24h)}$ values increased with dose in a less than dose proportional manner on day 1 of dosing. A 4-fold increase in dose (5-20 mg/kg/day) resulted in a 3.2-fold and 2.8-fold increase in C_{max} in males (7.35 vs 23.14 µg/mL) and females (6.11 vs 17.10 µg/mL), respectively, on first day of dosing. On first day of week 13, a 3.6-fold increase (7.35 vs 26.67 µg/mL) and a 4.1-fold increase (6.11 vs 25.29 µg/mL) in C_{max} was noted in males and females, respectively. Similar results were noted during weeks 39 and 52; systemic exposure was less than dose proportional. A 2-fold increase in dose (5-10 mg/kg/day) resulted a dose proportional systemic exposure (C_{max})

Drug Day	TK Parameter	Lacosamide (mg/kg)								
		5			10			20/25		
		M[a]	F[a]	F+M[b]	M[a]	F[a]	F+M[b]	M[a]	F[a]	F+M[b]
1	Cmax (µg/mL)	7.35	6.11	6.73 ± 1.04	12.14	9.97	11.05 ± 1.45	23.14	17.10	20.12 ± 5.03
	$AUC_{0\text{-}24h}$ (h.µg/mL)	18.4	21.0	1.89 ± 0.63	43.8	35.5	39.6± 6.8	95.6	68.6	82.1 ± 23.4
	Tmax (h)	1.0	1.5	1.3 ± 0.5	1.3	1.3	1.3 ± 0.9	1.0	1.5	1.3 ± 0.5
	$T_{1/2}$ (h)	1.52	2.26	1.89 ± 0.63	1.65	2.15	1.82 ± 0.53	2.0	2.06	2.03 ±
13	Cmax (µg/mL)	7.13	6.60	6.86 ± 0.82	13.35	14.55	13.95 ± 1.03	26.67	25.29	25.98 ± 4.78
	$AUC_{0\text{-}24h}$ (h.µg/mL)	22.8	23.0	22.9 ± 3.5	43.7	59.1	50.9 ± 9.2	124.4	128.8	126.6 ± 15.3
	Tmax (h)	1.0	1.0	1.0 ± 1.0	0.5	1.5	1.0 ± 0.7	1.5	2.0	1.8 ± 0.5
	$T_{1/2}$ (h)	2.33	2.31	2.32 ± 0.31	1.90	2.48	2.19 ± 0.44	2.13	2.36	2.28 ± 0.17
39	Cmax (µg/mL)	5.79	5.40	5.59± 1.01	14.48	12.68	13.58 ± 1.16	29.85	27.37	28.61 ± 6.25
	$AUC_{0\text{-}24h}$ (h.µg/mL)	19.8	21.0	20.4 ± 3.6	74.1	49.8	62.0 ± 14.5	166.4	133.2	149.8 ± 24.6
	Tmax (h)	1.5	1.3	1.4 ± 0.8	0.5	1.0	0.8 ± 0.3	1.0	1.5	1.3 ± 0.5
	$T_{1/2}$ (h)	2.34	2.43	2.38 ± 0.25	NA	2.47	2.47 ± 0.02	2.60	2.45	2.53 ± 0.16
52	Cmax (µg/mL)	7.07	7.36	7.22 ± 0.85	15.52	13.15	14.33 ± 2.04	23.86	18.88	21.37 ± 3.36
	$AUC_{0\text{-}24h}$ (h.µg/mL)	31.4	24.5	27.9 ± 6.9	71.0	54.6	62.8 ± 13.9	142.2	124.3	133.2 ± 15.5
	Tmax (h)	0.5	1.3	0.9 ± 0.8	0.8	1.3	1.0 ± 0.7	1.3	1.0	1.1 ± 0.6
	$T_{1/2}$ (h)	2.33	2.35	2.34 ± 0.35	2.69	2.37	2.53 ± 0.38	2.39	2.25	2.32 ± 0.17
Week	Ratio C_{max} (%)	97	120	108 ± 15	128	131	130 ± 15	87	89	88 ± 19

52/day 1	Ratio AUC (%)	172	120	146 ± 40	162	152	157 ± 10	121	108	136 ± 37

a: All values are given as median
b: All values are given as mean

Mortality: No treatment-related deaths occurred; all animals survived until schedule study termination.

Clinical signs: No treatment-related clinical signs were observed in the low- (5 mg/kg/day) and mid-dose (10 mg/kg/day) groups. Treatment-related clinical signs were observed in the high dose group. Mild toxicity signs were observed on isolated days in some dogs during the first 5-weeks of dosing when the high dose was 20 mg/kg/day. Vomiting (once or repeated episodes) was the primary clinical sign observed. Vomiting events occurred within 20 minutes to 1 hour after dosing on day 1 of treatment. In contrast to episodes of vomiting occurring on the first day of dosing, incidences of tonic/clonic, sedation, and ataxia did not occur until after the 20^{th} dose.

Due to the mild clinical signs observed following 20 mg/kg/day dose, the dose of lacosamide was increased to 25 mg/kg/day at the beginning of week 6 (day 36). Tonic-clonic convulsions, ataxia, reduced motility, tremor and increased salivations were the primary treatment-related clinical signs noted after increasing the dose of lacosamide. Tonic-clonic seizure was noted in one dog on the first day (D36) of treatment presented. Convulsions were observed in one to six dogs from days 36 to 364. The number of dogs presenting with seizures increased as the number of exposures to the test drug increased. These results suggest that lacosamide has pro-convulsant properties and that repeative exposures increased the animal's sensitivity to its pro-convulsant properties. Because the Sponsor did not provide individual data on clinical signs, it was not possible to ascertain if certain dogs were more sensitive to the pro-convulsant properties of lacosamide.

Ataxia, reduced motility, tremors, and increased salivation, and sedation were other treatment-related clinical signs observed in individual dogs. Most of the dogs revealed ataxia, reduced motility, tremors and/or salivation from test week 15 to 16 onwards; occurring on most to all days of the week. Abdominal and/or lateral position was observed occasionally between treatment weeks 9 and 29. The clinical signs occurred between 5 and 60 minutes after oral dosing and lasted up to 2 hours. The increased salivation was noted for 24 hours after dosing.

Body weights: No treatment-related changes in body weights were observed.

Food consumption: Food consumption was measured daily and weekly relative to control. Compared to controls food intake a significant difference ($p \leq 0.01$) was noted in females at weeks 7 and 24. At week 7, females in the 10 mg/kg/day group displayed a 30% increase in food consumption. Females treated with 20/25 mg/kg/day of lacosamide displayed a 20% decrease in food intake. These changes were not considered toxicologically relevant. According to the Sponsor, these changes were considered to be within the normal range.

Ophthalmoscopy: Examination of the eyes and optic region at treatment weeks 13, 26, 39, and 52 did not show any apparent test-article related effects. Also no treatment-related effects were observed at the end of the 4-week recovery period. However, one male animal, in the high dose group, did present with redness and discharge of the eye of minimal degree during week 9 examination. This is considered coincidental and not toxicologically relevant.

EKG: The heart rate of the lacosamide treated males and females in the mid- and high-dose groups were slightly higher than that of the control 2 hours after dosing on weeks 13, 26, 39 and 52 (Table 1). The difference from the control was between plus 2% to 36%. However, these changes were not statistically significant (at $p \leq 0.01$) or dose-dependent.

Relative to the control (247.3 ± 21.2), females in the high dose group (287.0 ± 21.5) had a slightly but statistically significant ($p \leq 0.01$) higher QTC value, as calculated according to the Fridericia formula, on test day 1. The difference from the control was plus 16%. This increase was contributed to one dog having a relatively low QT_c value. The Sponsor considered the QT_c value to be within the normal range.

No treatment-related changes were observed in QRS interval, QT interval, PQ interval, P-segment and QT_c (according to Van de Water formula) electrocardiographic complexes in either males or females.

No changes in heart rate, and the duration of PQ, QRS, QT, QT_c and P-segment were observed at the end of the 4-week recovery period.

Table 1. Heart rate recording in dogs 2 hours following oral lacosamide at doses of 5, 10 and 25 mg/kg/day.

	Heart Rate (beats/min) ± S.D. (% change from control)							
	Dose (mg/kg/day)							
Treatment Week	**0**		**5**		**10**		**25**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
13	96.7 ± 14.5	89.9 ± 17.1	102.7 ± 15.6 (+6%)	77.1 ± 8.3 (-14%)	89.9 ± 14.0 (-7%)	101.4 ± 15.4 (+13%)	115.6 ± 12.2 (+20%)	98 ± 26.5 (+9%)
26	96.4 ± 10.7	94.3 ± 19	94.7 ± 15.5 (-2%)	91 ± 31.5 (-6%)	95.13 ± 17.9 (+5%)	93.4 ± 15.4 (-1%)	96.9 ± 14 (+7%)	117.7 ± 20.9 (+25%)
39	87.1 ± 15	84.1 ± 27.0	88.7 ± 13.5 (+2%)	90.7 ± 22.3 (+8%)	93.1 ± 16 (+7%)	100.4 ± 23 (+19%)	108.3 ± 21.3 (+24%)	114.3 ± 20.0 (+36%)
52	83.1 ± 27.5	85.4 ± 32.3	84.9 ± 6.8 (+2%)	84.7 ± 27.3 (-1%)	97.0 ± 22.8 (+17%)	86.4 ± 26.9 (+2%)	100.4 ± 27.3 (+ 21%)	105.3 ± 30.8 (+23%)

Treatment-related effects on peripheral arterial blood pressure were observed in both males and females. Marginal but statistically significant ($p \leq 0.01$) decrease in blood pressured was observed in male dogs in the 10 mg/kg/day on test day 3 (38%). During week 26, a significant increase in blood pressure was observed in the males in the high dose group (18%). Compared to control, there were no treatment-related effects on peripheral arterial blood pressure in males treated with 5 mg/kg/day of lacosamide on test days 1 and 3 and test weeks 13, 39 and 52.

Table 2. Peripheral arterial blood pressure measure difference relative to control in male dogs before and 2.5 hours following oral lacosamide at doses of 5, 10 and 20/25 mg/kg/day.

	Peripheral Arterial Blood Pressure (mm Hg) ± S.D. (% change from control)							
	Dose (mg/kg/day)							
Test	**0**		**5**		**10**		**20/25[A]**	
	Before	**Post-dosing**	**Before**	**Post-dosing**	**Before**	**Post-dosing**	**Before**	**Post-dosing**
Day 1	150.0 ± 18.6	144.6 ± 13.9	166.0 ± 18.7 (+11%)	158.9 ± 21.7 (+18%)	173.6 ± 7.5 (+16%)**	153.4 ± 16.6 (+6%)	155.0 ± 22.2 (3%)	144.4 ± 17.7 (-0.1%)
Day 3	146.6 ± 9.9	140.6 ± 7.8	137.9 ± 21.2 (-6%)	128.4 ± 17.8 (-9%)	133.4 ± 13.0 (-9%)	100.9 ± 19.6 (-28%)**	135.6 ± 16.2 (-8%)	132.0 ± 51.9 (-6%)
Week 26	145.3 ± 12.1	131.0 ± 8.5	139.1 ± 13.2 (-4%)	138.6 ± 14.1 (-5%)	140.9 ± 14.1 (-3%)	139.9 ± 9.8 (+7%)	145.9 ± 8.6 (+0.4%)	154.4 ± 4.9 (+18%)**

Treatment-related decrease in peripheral arterial blood pressure was observed in females. On test day 1, a dose-dependent decrease was noted 2.5 hours following 10 and 20 mg/kg/day. Relative to control peripheral arterial blood pressure was significantly ($p \leq 0.01$) decreased by 30% and 35% following 10 and 20 mg/kg/day, respectively. Females in the high dose group (20/25 mg/kg/day) also presented with a significant decrease in blood pressure on before dosing and after dosing on test day 3 (before: 15%; after: 19%) and test week 13 (before: 31%; after: 37%). No changes in the peripheral arterial blood pressure were noted after week 13.

The Sponsor did not consider the changes in blood pressure in the males on test day 1 and test week 13, and the females in the 10 mg/kg (test day 1) to be treatment-related. The Sponsor considered these changes to be within the normal variability for the conscious dogs.

Table 3. Peripheral arterial blood pressure measure recording in female dogs before and 2.5 hours following oral lacosamide at doses of 5, 10 and 20/25 mg/kg/day.

	Peripheral Arterial Blood Pressure (mm Hg) ± S.D. (% change from control)							
	Dose (mg/kg/day)							
Test	**0**		**5**		**10**		**20/25[A]**	
	Before	**Post-dosing**	**Before**	**Post-dosing**	**Before**	**Post-dosing**	**Before**	**Post-dosing**

Day 1	145.9 ± 17.3	138.7 ± 27.1	158.3 ± 16.4 (+8.5%)	113.3 ± 21.7 (+18%)	159.3 ± 11.1 (+9%)	102. ± 11.0 (-30%)**	143.5 ± 20.2 (-2%)	90.1 ± 16.5 (-35%)**
Day 3	141.4 ± 8.7	128.9 ± 9.2	142.3 ± 13.0 (+0.6%)	118.4 ± 9.9 (-8%)	135.4 ± 16.7 (-4%)	116.9 ± 20.7 (-9%)	119.7 ± 9.9 (-15%)**	103.9 ± 4.159 (-19%)**
Week 13	145.7 ± 11.4	135.1 ± 13.6	142.1 ± 13.7 (-2.5%)	122.3 ± 9.4 (-10.5%)	133.3 ± 18.5 (-9%)	118.0 ± 19.7 (-13%)	100.4 ± 19.0 (-31%)**	84.6 ± 11.8 (-37%)**
Week 26	141.9 ± 7.3	158.9 ± 14.7	149.0 ± 12.1 (-5%)	178.9 ± 16.0 (-13%)	149.9 ± 14.1 (+6%)	163.3 ± 13.6 (+3%)	155.7 ± 14.5 (+10%)	144.0 ± 16.1 (-9%)
Week 39	135.7 ± 15	117.1 ± 21.4	122.1 ± 20.1 (-10%)	126.4 ± 15.3 (+8%)	126.9 ± 15.1 (-6.5%)	134.6 ± 12 (+15%)	114.0 ± 22.2 (-16%)	123.6 ± 24.8 (+6%)
Week 52	153.1 ± 9.7	149.9 ± 9.5	156.6 ± 14.0 (+2.3%)	148.4 ± 14.8 (-3%)	166.7 ± 20.0 (+9%)	162.1 ± 31.1 (+8%)	161.0 ± 28.3 (+ 5%)	166.1 ± 14.5 (+11%)

A: On day 1 and day 3, the high dose of lacosamide was 20 mg/kg. During weeks 13, 26, 39 and 52, the high dose was 25 mg/kg/day.
**: significant at $p \leq 0.01$

Hematology: A complete hematological assessment was performed prior to first dosing, at the end weeks 13, 26, 39, 52 and 56. No statistically significant changes in the blood parameters measured were observed in the lacosamide treated groups compared to the controls.

Clinical chemistry: A complete clinical chemistry assessment was performed prior to first dosing, at the end weeks 13, 26, 39, 52 and 56. With the exception of plasma levels of bile acids; no statistically significant changes in the blood parameters measured were observed in the lacosamide treated groups compared to the controls. A mild but statistically significant increase ($p \leq 0.01$) in the plasma levels of bile acids in the high-dose females; was observed at the end of test week 39. Plasma level of bile acid was 6.77 and 16.86 µmol/L serum for the control and high dose group. This represents a 149% increase. Because change in plasma bile level was not dose-related, this change is considered incidental/not toxicologically significant.

Urinalysis: Urinalysis was performed prior to first dosing, at the end weeks 13, 26, 39, 52 and 56. No differences in the urine parameters between control and treated groups of either sex were observed during the treatment periods at the end of the recovery periods.

However, some treatment-related changes were observed in females. At week 26, females treated with 5 mg/kg/day of lacosamide had an average pH of 7.0 (+11%) compared to an average of 6.3 for the control group. At week 52, the urine volume of females treated with 10 mg/kg/day of lacosamide was significantly increased; 143 mL/kg/24 hr (=57%) compared to 91.3 mL/kg/24 hr for the control females. The Sponsor considered these changes to be within the normal range. The reviewer concurs.

Gross pathology: No drug-related changes were observed.

Organ weights: No drug-related changes on absolute and relative organ weight were observed in lacosamide-treated animals compared to control treated animals. Also, no treatment-related changes were noted in the organ weight and organ/brain ratio at the end of the 4-week recovery period.

Histopathology: No drug-related findings were observed at Week 52.

Other: No treatment-related impairment to auditory acuity was observed.

2.6.6.4 Genetic toxicology

The Sponsor conducted five genetic toxicology studies to evaluate the genotoxicity and/or mutagenicity of lacosamide. Three of the five studies were in vitro studies and the remaining 2 studies were in vivo Dr. Edward Fisher reviewed these studies. Specific details can be found in the NDA (NDA № 22-253) review prepared by Dr. Fisher.

2.6.6.5 Carcinogenicity

To evaluate the carcinogenic potential of lacosamide, the Sponsor conducted a 2-year carcinogenicity bioassays were in mice and rats. Drs. Edward Fisher and Terry Peters reviewed these studies. Specific details of these studies can be found in NDA 22-253 review from Drs. Fisher and Peters.

2.6.6.6 Reproductive and developmental toxicology

The Sponsor conducted a standard battery of reproductive toxicology studies. Dr. Edward Fisher reviewed these studies. Specific details of these studies can be found in NDA 22-253 review from Dr. Fisher.

2.6.6.9 Discussion and Conclusions

See overall conclusions below.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the Sponsor]

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Lacosamide has been adequately characterized in nonclinical pharmacokinetic and toxicologic studies including repeat-dose toxicology, genetic toxicology, carcinogenicity, and reproductive toxicology studies such that the risks for human use may be adequately judged. Based on the No Adverse Effect Levels (NOAELs) in the pivotal repeat-dosing toxicology studies, a small margin of exposure or safety for human use was noted. The NOAELs were 60, 90 and 10 mg/kg/day in mice, rats and dogs after once daily oral administration of lacosamide for 3, 6 and 12 months, respectively. The dog was slightly more sensitive to lacosamide than rodents. Based on the C_{max} at the NOAEL, the safety margins calculated from the mouse, rat and dog was, 1.9 and 1.0 (male) and 0.9 (female), respectively.

The toxicities associated with oral administration of lacosamide primarily were CNS-related consistent with an exaggerated pharmacologic effect. The observed CNS clinical signs occurred at the C_{max}. Dose-dependent CNS-related clinical signs observed in rodent include muscle flaccidity, reduced motility, hypoactivity, apathy, impaired or lost righting reflex, splayed limbs, ataxia, abdominal and/or lateral position, dyspnea, polypnea or bradypnea, prostration, increased muscle tone, convulsions as well as cold to the touch and excess salivation. Similarly, dose-dependent CNS effects observed in the dog included ataxia/loss of coordination, abdominal and/or lateral position, lateral recumbency, limited use of hind limbs, hypoactivity, reduced motility, sedation, lethargy, restlessness, salivation, and convulsions.

Unresolved toxicology issues (if any): There are no unresolved toxicology issues based upon review of the repeat-dose toxicology studies described here. See Dr. Fisher's review for unresolved concerns regarding the reproductive toxicology studies.

Recommendations: From the nonclinical pharmacology/toxicology perspective, based upon the information reviewed by this reviewer, this NDA may be approved.

Suggested labeling: See labeling recommendations from Dr. Ed Fisher for NDA 22-253.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

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

/s/

Belinda Hayes
6/5/2008 02:53:42 PM
PHARMACOLOGIST

R. Daniel Mellon
6/5/2008 03:15:25 PM
PHARMACOLOGIST
In concur.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: May 9, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Evaluation of Abuse Potential of Vimpat (lacosamide) b(4)
Labeling Recommendations
NDAs 22-253, 22-254, —
Indication: Treatment of Partial-Onset Seizures (200, 400, — mg)
Sponsor: Schwarz Biosciences, Inc.

Summary:

This CSS consult evaluates the abuse potential of lacosamide (NDAs 22-253, 22-254 —
as requested by the Division of Neurology Products, to help determine appropriate labeling and b(4)
scheduling of the drug. Lacosamide is concurrently being reviewed in the Division of
Anesthesia, Analgesia and Rheumatology Products under NDA — for the treatment of
diabetic neuropathic pain. Lacosamide is not currently marketed in any country.

After evaluating the abuse related data submitted in the NDA, CSS concludes that lacosamide has abuse potential. CSS is preparing an Eight Factor Analysis that recommends placement of lacosamide into Schedule IV of the Controlled Substances Act (CSA). The Sponsor should be made aware that CSS is recommending scheduling of lacosamide and that lacosamide cannot be marketed, if the NDA is approved, until the scheduling action is complete. The scheduling process requires that the scheduling recommendation be approved by the FDA Commissioner and the Assistant Secretary for Health at HHS prior to Drug Enforcement Administration (DEA) notice of proposed rulemaking and final action.

Background:

b(4)

Lacosamide is a new molecular entity that —
Lacosamide has affinity for the sodium channel and the collapsin response mediator protein 2

b(4)

(CRMP-2), which previously have not been specifically identified to be associated with abuse potential. ——

b(4)

Conclusions:

Upon review of human test data in the NDA, CSS concludes that lacosamide has abuse potential similar to that of alprazolam, a Schedule IV drug under the CSA. This conclusion is based on the following data (see Table 1 below in Summary of Data from Abuse-Related Studies in NDA):

1. In a human abuse potential study with individuals who had a history of abusing central nervous system depressants (Study #SP903), 200-800 mg lacosamide produced positive subjective responses on visual analog scales that were statistically significantly different from placebo but not statistically distinguishable from positive subjective responses produced by alprazolam, a Schedule IV drug.

2. A high mean rate of euphoria-type adverse events (AEs) were observed in a Phase 1 human abuse potential study comparing lacosamide to alprazolam (Study # SP903), in two Phase 1 pharmacokinetic studies (Study # SP587 and SP588) and in a Phase 1 electrocardiographic study (Study #SP640)

3. The observance of euphoria-type AEs in Phase 2/3 double-blind and open-label clinical efficacy studies for partial onset seizure (Study # SP667, SP754, SP755, SP586, SP598, SP607, SP615, SP756, SP774) and diabetic neuropathic pain (Study #SP614, SP742, SP743, SP768, SP 665, SP745, SP746, SP830) is difficult to interpret in terms of their direct relationship to lacosamide, since all patients were concomitantly taking other centrally-acting medications during the studies.

4. In an animal drug discrimination study (Study #05.237/5) between lacosamide and alprazolam, phenobarbital and morphine, partial generalization was observed. Lacosamide was unable to produce self-administration or conditioned place preference in animals (Study # 05.673/4 and 05.122/6). This result in rats was not consistent with the ability of lacosamide to produce euphoria in humans. However, not all drugs with known abuse potential in humans are self-administered by animals, especially when there is a unique mechanism of action like that of lacosamide.

5. Lacosamide does not appear to produce physical dependence, based on the lack of an observed withdrawal syndrome following abrupt discontinuation of the drug in animal and human studies (Study #SP746 and #RS211).

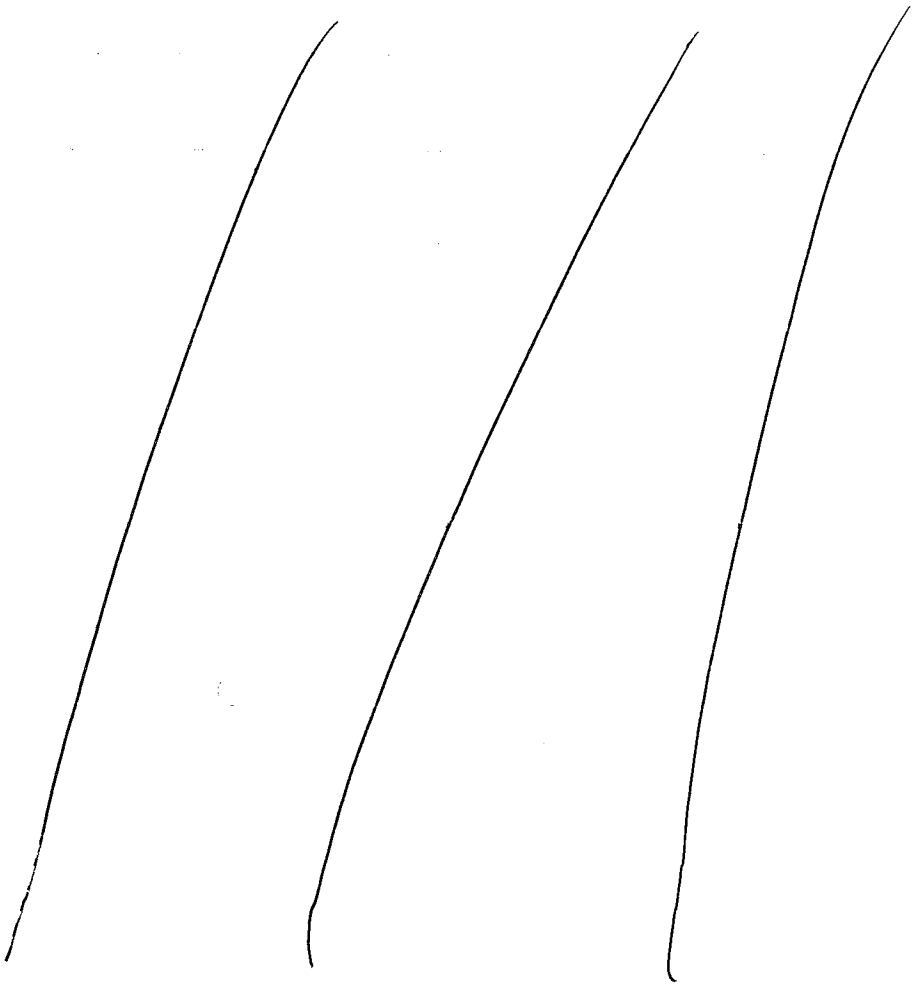
Recommendations:

1. Based on the profile of effects in animal and human studies following lacosamide administration, CSS recommends ——

b(5)

b(4)

2. CSS has reviewed the label text proposed by the Sponsor and recommends revisions, based on our evaluation of the abuse potential data submitted in the NDA. Below is a proposed revised label text, as it relates to abuse potential.



b(4)

Summary of Data from Abuse-Related Studies in NDA

The following is a summary of data from abuse-related studies conducted with lacosamide that form the basis of the CSS recommendation for scheduling:

Phase 1 Clinical Data

The incidence of euphoria-type AEs in Phase 1 clinical studies was evaluated. Four Phase 1 studies (Study #SP903, SP587, SP588 and SP640) were found to contain euphoria-type AEs. These studies are detailed below in Table 1.

Table 1: Phase 1 Studies in Which Euphoria-Type AEs Were Observed

Study Number	SP903	SP587	SP588	SP640
Study Type	Human Abuse Potential Study	Pharmacokinetics: Single Dosing	Pharmacokinetics: Single and Multiple Dosing	Electrocardio-graphic Study
Study Design	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled
Subjects	Drug abusing subjects	Healthy subjects	Healthy subjects	Healthy subjects
Number of Subjects	N = 30	N = 16	N = 31	N = 220
Drug Dosing	Single, oral doses of lacosamide (200 and 800 mg), alprazolam (1.5 and 3.0 mg) and placebo	Lacosamide (single oral doses of 400, 600 or 800 mg) or placebo	Lacosamide (single oral doses of 300 and 500 mg) or placebo, followed by lacosamide (multiple oral doses of 300, 400, 500 mg for 16 days) or placebo	Lacosamide (oral 400 or 800 mg/day for 6 days), moxifloxacin (oral 400 mg/day for 3 days) or oral placebo (for 6 days)
Study Results	Positive responses on subjective measures of rewarding effects after single oral doses of 200-800 mg lacosamide, 1.5 and 3.0 mg alprazolam, Euphoria-type AEs in 15% of subjects after 800 mg lacosamide, in 12% of subjects after 1.5 mg alprazolam and 3% of subjects after placebo.	Euphoria-type AEs after single oral doses of lacosamide reported in 22% of subjects after 800 mg , in 8% after 600 mg, and 25% after 400 mg, compared to 0% after placebo.	Euphoria-type AEs after single oral doses of lacosamide reported in 10% of subjects after 500 mg, 7% after 300 mg and 0% after placebo; also after multiple doses in 0% after 500 mg, 29% after 400 mg, in 17% after 300 mg and 0% after placebo.	Euphoria-type AE of "Feeling Drunk" reported after single oral doses of lacosamide in 16% after 800 mg and in 8% after 400 mg, compared to 3% after placebo and 0% after moxifloxacin.

* Euphoria-type AEs were reported in a Phase 1 human abuse potential study (Study #SP903) in individuals with a history of abusing CNS depressants. In this study, 800 mg of lacosamide produced subjective responses on scales measuring "High", "Euphoria", "Drug Liking", "Good Drug Effect" and "Sedation" that were not statistically distinguishable from the subjective responses on the same scales following administration of 1.5 mg alprazolam, a Schedule IV drug. Euphoria was reported as an AE in 5 of 35 subjects (15%) who received the 800 mg dose of lacosamide, in 4 of 34 subjects (12%) who received 1.5 mg alprazolam and in 1 of 34 subjects (3%) who received placebo. These data demonstrate that the abuse potential of lacosamide is similar to that of alprazolam.

* The AE "Euphoria" was reported in two pharmacokinetic (PK) studies (Study #SP587 and SP588) in healthy individuals. In one of the PK studies, euphoria was reported in 2 of 9 (22%) of subjects who received an 800 mg dose, in 1 of 12 (8%) of subjects who received a 600 mg dose and in 3 of 12 (25%) of subjects who received a 400 mg dose, compared to 0 of 12 (0%) of pooled subjects who received placebo. In another PK study, euphoria was reported in 1 of 10 (10%) of subjects who received 500 mg lacosamide in a single dose and in 1 of 14 (7%) of subjects who received 300 mg lacosamide in a single dose, compared to 0 of 9 (0%) of pooled subjects who received placebo. When the subjects in this second study subsequently received multiple doses of lacosamide, euphoria was reported in 0 of 4 (0 %) of subjects in the 500 mg group, in 2 of 7 (29%) in the 400 mg group and in 2 of 12 (17%) of subjects in the 300 mg group, compared to 0 of 8 (0%) of pooled subjects who received placebo.

* A euphoria-type AE was reported in a Phase 1 electrocardiographic study (Study #SP640) with healthy individuals. The AE "Feeling Drunk" was reported in 11 of 71 subjects (16%) who received the 800 mg dose of lacosamide, in 5 of 60 subjects (8%) who received the 400 mg dose of lacosamide, in 2 of 62 subjects (3%) who received placebo and 0 of 54 subjects (0%) who received the moxifloxacin (the positive control drug known to prolong QTc interval).

Preclinical Data

* In a rat drug discrimination study (Study #05.237/5) lacosamide produced partial generalization to two CNS depressant drugs (alprazolam, phenobarbital; Schedule IV) and to morphine (Schedule II).

Evaluation of Physical Dependence in Humans and Animals

* A prospective evaluation of physical dependence (Study #SP746) was conducted in diabetic neuropathic pain patients who had been treated with oral doses of lacosamide at 200 and 400 mg/day for at least one year and then abruptly discontinued from lacosamide. Few AEs were observed during the 4-week discontinuation period, with the exception of re-emergence of disease symptoms. No signs or symptoms indicative of a withdrawal syndrome were observed that could be indicative of the presence of physical dependence.

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* Physical dependence was assessed in rats and dogs (Study # RS211) that had participated in toxicity studies by observing behaviors in the animals following abrupt drug discontinuation. Neither species exhibited behaviors associated with a withdrawal syndrome in the period following lacosamide discontinuation that would be indicative of physical dependence.

APPENDIX

EVALUATION OF ABUSE -RELATED DATA WITH LACOSAMIDE

This appendix provides the CSS evaluation of the abuse potential-related data on lacosamide submitted in NDAs 22-253, 22-254, —— as described in the index below: b(4)

Index of Studies

b(4)

I. Summary of Data Related to Abuse Potential from Human Studies

A. Euphoria-Type AEs in a Phase 1 Human Abuse Potential Study (Study #SP903)

Conclusion

Oral administration of lacosamide produced a high rate of subjective responses and euphoria-type AEs that were statistically indistinguishable from alprazolam, a Schedule IV drug.

Study Design, Subjects and Drug Treatments

A human abuse potential study was conducted in individuals with a history of recreational CNS depressant abuse who had at least 10 lifetime experiences with benzodiazepines, barbiturates or GHB and at least one recreational use of a CNS depressant in the past month.

Prior to selection for participation in the Treatment Phase of the study, 73 potential subjects underwent a Qualifying Phase in which individuals received single oral doses of 2.0 mg alprazolam (4 – 0.5 mg capsules) and placebo (4 placebo capsules) in randomized order, to determine if they were able to differentiate between the two treatments. The two trials were conducted on consecutive days with at least 24 hours separating treatments. The narrative notes that there was "no washout". The half-life of alprazolam is ~8-20 hours and it typically takes 4-5 half-lives before termination of a biological effect. Thus, if alprazolam was the first treatment, there could be carryover effects in the placebo session that could skew the subjective responses observed.

Alprazolam was chosen as the positive control because it is known to have anticonvulsant effects (which is a therapeutic claim of lacosamide), because it has similar pharmacokinetics to lacosamide (the half-life is ~13 hours for lacosamide) and no active metabolites. The 2 mg dose of alprazolam was chosen based on its use in previous human abuse potential studies as a dose that differentiates from placebo on positive subjective measures.

Forty-eight subjects who were able to "distinguish" between alprazolam and placebo were deemed qualified to enter the Treatment Phase, but only 38 subjects participated in the Treatment Phase. No information was provided regarding the criteria used to determine which subjects could "distinguish" between alprazolam and placebo, but the same subjective measures were used in both the Qualifying Phase and the Treatment Phase (see below).

The narrative notes that 11 of the 38 subjects who were allowed to participate in the Treatment Phase did not actually meet qualification criteria:

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* 6 subjects did not have a peak score on the Overall Drug Liking variable analog scale (VAS) in response to 2 mg alprazolam that was greater than that of placebo.
* 4 subjects did not have "an appropriate pharmacological response on 7 measures"
* 1 subject failed to qualify on either peak score on Overall Drug Liking or on "appropriate pharmacological response".

A total of 30 of the 38 subjects who entered the Treatment Phase completed all study procedures. It is unclear from the information provided how many of the completers included the 11 subjects who did not meet qualification criteria.

The Treatment Phase was a randomized, double-blind, crossover design in which subjects received five oral treatments: lacosamide (200 and 800 mg), alprazolam (1.5 and 3.0 mg) and placebo. The 200 mg dose of lacosamide represents the lowest of —proposed therapeutic doses being tested in clinical efficacy trials (ie: 200, 400 —— mg). The narrative states that the 800 mg dose represents "4-times the therapeutic dose", —— b(4)

As noted above, alprazolam was chosen as the positive control because it is known to have anticonvulsant effects (which is a therapeutic claim of lacosamide), because it has similar pharmacokinetics to lacosamide (the half-life is ~13 hours for lacosamide) and no active metabolites. The 1.5 and 3.0 mg doses of alprazolam were chosen based on their use in previous human abuse potential studies as doses that differentiates from placebo on positive subjective measures. These alprazolam are within the high end of recommended therapeutic doses.

All drug treatments in the Treatment Phase were overencapsulated using 100 mg lacosamide tablets and 0.5 mg alprazolam tablets. Each treatment session was separated by a washout period of at least 5 days. Subjects were fasted "until 2 hours after administration of trial medication".

Subjective measures were taken at 0.5, 1.0, 2, 3, 4, 6, 8, 10, 12 and 24 hours following treatment administration. Primary subjective measures included visual analog scales (VAS) for Drug Liking, Overall Drug Liking, High and the Addiction Research Center Inventory (ARCI) subscale for Phenobarbital-Chlorpromazine-Alcohol Group (PCAG) (assessing CNS depressant effects). Secondary subjective measures included VAS for Take Drug Again, Any Drug Effect, Good Drug Effects, and Bad Drug Effects as well as ARCI subscales for Morphine-Benzedrine Group (MBG) (assessing euphoria) and Lysergic Acid Diethylamide (LSD) (assessing dysphoria or hallucinogenic effects). Supportive subjective measures included ARCI subscales for Amphetamine and for Benzedrine Group (BG), as well as VAS for nausea.

Pharmacokinetics were evaluated with blood draws at baseline, 2, 4, 8, and 12 hours following treatment administration.

Monitoring of safety measures included AEs reported by the subject or observed by the investigator, changes in "laboratory parameters" and physical examination, changes in vital signs (blood pressure, pulse rate, oxygen saturation and respiration rate) and changes in electrocardiogram (ECG). Monitoring continued for 8 hours after treatment administration.

Subjective Measure Results

Eight measures that assess abuse potential (Table 2 below) depicts peak subjective responses during the study monitoring period for placebo, alprazolam (1.5 and 3.0 mg) and lacosamide (200 and 800 mg):

Table 2: Subjective Responses During Human Abuse Potential Study

Scale	Placebo	Alprazolam (1.5 mg)	Alprazolam (3.0 mg)	Lacosamide (200 mg)	Lacosamide (800 mg)
High	14.4 ± 26.1	78.8 ± 22.7 *	87.8 ± 12.1 *	52.5 ± 32.8 *	82.2 ± 20.2 *
Euphoria / ARCI-MBG	0.7 ± 1.6	4.3 ± 3.8 *	6.1 ±3.9 *	2.2 ± 3.4 *	4.0 ± 5.1 *
Good Drug Effects	35.6 ± 29.9	82.3 ± 17.2 *	88.0 ± 13.2 *	56.7 ± 29.8	73.6 ± 26.0 *
Drug Liking	4.1 ± 11.7	29.3 ± 14.1 *	35.6 ± 16.1 *	13.4 ± 14.6 *	23.2 ± 21.3 *
Overall Drug Liking	-2.3 ± 18.1	26.9 ± 24.6 *	32.4 ± 22.0 *	3.7 ± 22.7	-5.4 ± 35.1
Sedative / ARCI-PCAG	1.3 ± 2.3	6.9 ± 2.2 *	7.3 ± 2.7 *	2.0 ±2.3	7.8 ± 2.7 *
Take Drug Again	39.3 ± 27.4	85.7 ± 24.3 *	86.9 ± 20.3 *	58.6 ± 32.2 *	44.8 ± 38.8
Bad Drug Effects	15.3 ± 25.2	29.1 ± 25.1 *	41.3 ± 27.3 *	25.2 ± 28.8	66.4 ± 30.8 *

* = $p < 0.01$ compared to placebo

Alprazolam at 1.5 mg and 3.0 mg was statistically significantly greater than placebo on all positive subjective measures. These results validate the study and demonstrate that drug abusing subjects report that a Schedule IV drug of abuse produces rewarding effects under experimental conditions. Additionally, there was also a statistically significantly greater response for both alprazolam doses on the "Bad Drug Effects" scale compared to placebo.

When lacosamide was tested, both doses produced a statistically significant increase compared to placebo on most positive subjective scales. For the 200 mg dose of lacosamide, there was a statistically significantly greater subjective response compared to

placebo on the scales "High", "Euphoria/MBG", "Drug Liking" and "Take Drug Again". For the 800 mg dose of lacosamide, there was a statistically significantly greater subjective response compared to placebo on the scales "High", "Euphoria/MBG", "Good Drug Effects", "Drug Liking", "Sedative/PCAG". Additionally, the 800 mg dose of lacosamide also produced a statistically greater response compared to placebo on "Bad Drug Effects".

When the 200 mg dose of lacosamide was compared to alprazolam, the lower dose of lacosamide produced responses on all positive subjective measures that were statistically significantly less than the responses from both the 1.5 and 3.0 mg doses of alprazolam.

In contrast, when the 800 mg dose of lacosamide was compared to alprazolam, a different pattern emerged than that seen with the 200 mg dose of lacosamide. Specifically, the 800 mg dose of lacosamide did not produce positive subjective responses that were statistically significantly less than those produced by the 1.5 mg dose of alprazolam on measures of High, Euphoria MBG, Drug Liking, Good Drug Effects and Sedation PCAG. Similarly, the 800 mg dose of lacosamide did not produce positive subjective responses that were statistically significantly less than those produced by the 3.0 mg dose of alprazolam on measures of High, Good Drug Effects and Sedation PCAG. Thus, these data demonstrate that the 800 mg dose of lacosamide produces positive subjective effects that are similar to those produced by alprazolam.

AEs Reported During Human Abuse Potential Study

Table 3 (below) depicts AEs observed during the study that are possibly reflective of abuse potential as shown below for placebo, alprazolam (1.5 and 3.0 mg) and lacosamide (200 and 800 mg):

Table 3: AEs Related to Abuse Potential During Human Abuse Potential Study
(number of subjects with AE/total number of subjects, percent in parentheses)

Adverse Event	Placebo	Alprazolam (1.5 mg)	Alprazolam (3.0 mg)	Lacosamide (200 mg)	Lacosamide (800 mg)
Euphoria	1 of 34 (3%)	4 of 34 (12%)	3 of 33 (9%)	1 of 35 (3%)	5 of 35 (15%)
Somnolence	5 of 34 (15%)	26 of 34 (77%)	33 of 33 (100%)	10 of 35 (29%)	18 of 34 (53%)
Visual Disturbance	0 of 34 (0%)	1 of 34 (3%)	0 of 33 (0%)	0 of 35 (0%)	6 of 34 (18%)
Hearing Impaired "altered auditory perception"	0 of 34 (0%)	0 of 34 (0%)	1 of 33 (3%)	0 of 35 (0%)	5 of 34 (15%)

As would be expected from a Schedule IV drug, alprazolam produced a high rate of euphoria at 1.5 mg (4 of 34 subjects; 12%) and at 3.0 mg (3 of 33 subjects; 9%), compared to placebo (1 of 34 subjects; 3%). Notably, however, 800 mg lacosamide produced a rate of euphoria (5 of 35 subjects; 15%) that was greater than that produced by either dose of alprazolam. The euphoria observed following 800 mg lacosamide was mild or moderate in intensity and lasted between 1-11 hours in duration. In contrast, the 200 mg dose of lacosamide produced a rate of euphoria (1 of 35 subjects; 3%) that was equivalent to that seen with placebo.

Alprazolam produced a high rate of somnolence at 1.5 mg (26 of 34 subjects; 77%) and at 3.0 mg of alprazolam (33 of 33 subjects; 100%). Lacosamide also produced a high rate of somnolence at 200 mg (10 of 35 subjects; 29%) and at 800 mg (18 of 34 subjects; 53%). In contrast, 5 of 34 subjects (15%) who received placebo reported somnolence.

Visual disturbances were reported in 6 of 34 subjects (18%) who received 800 mg lacosamide and in 1 of 34 subjects (3%) who received 1.5 mg alprazolam (3%), but were not observed following 3.0 mg alprazolam (0 of 33 subjects; 0%), 200 mg lacosamide (0 of 35 subjects; 0%) or placebo (0 of 34 subjects; 0%). Hearing impairment (also coded as "altered auditory perception") was reported in 5 of 34 subjects (15%) who received 800 mg lacosamide and in 1 of 33 subjects (3%) who received 3.0 mg alprazolam (3%), but was not reported after 200 mg lacosamide (0 of 35 subjects; 0%), 1.5 mg alprazolam (0 of 34 subjects; 0%) or placebo (0 of 34 subjects; 0%).

Pharmacokinetic Results

The 200 mg dose of lacosamide produced a Cmax of 4 µg/ml, while the 800 mg dose of lacosamide produced a Cmax of 18 µg/ml. These results show that the Cmax of lacosamide is approximately dose-proportional. The Tmax in this study was 2 hours, but given that no blood draws occurred prior to this timepoint, it is unclear if the Cmax occurred earlier. Plasma levels declined in a linear fashion over time from the 2 hours timepoint.

Notably, 9 of 30 subjects (30%) had measurable levels of lacosamide during treatment periods in which no lacosamide was administered. Eight of these 9 subjects had received the 800 mg dose of lacosamide in the previous treatment period, with plasma levels ranging from 0.039 µg/ml to 5.3 µg/ml. The study narrative attributes this to a possible error in treatment administration resulting from inadvertent administration of 200 mg lacosamide instead of the scheduled dose of 1.5 mg alprazolam.

B. Euphoria-Type AEs in Phase 1 Pharmacokinetic Studies (Study #SP587, SP588)

Conclusion

Oral administration of lacosamide produced a high rate of the AE "Euphoria" in two Phase 1 PK studies in which lacosamide was the only drug administered to healthy subjects.

PK Study 1

In a study evaluating the pharmacokinetics of single-dose oral lacosamide, euphoria was reported as an AE in 2 of 9 subjects (22%) who received an 800 mg dose, in 1 of 12 subjects (8%) who received a 600 mg dose and in 3 of 12 subjects (25%) who received a 400 mg dose, compared to 0 of 12 of pooled subjects (0%) who received placebo.

PK Study 2

Euphoria was reported as an AE in a study evaluating the pharmacokinetics of single dose and repeated dose lacosamide. In the single dose phase of the study, euphoria was reported in 1 of 10 subjects (10%) who received 500 mg lacosamide and in 1 of 14 subjects (7%) who received 300 mg lacosamide, compared to 0 of 9 of pooled subjects (0%) who received placebo. When these subjects received lacosamide in multiple doses, euphoria was reported in 0 of 4 subjects (0 %) in the 500 mg group, in 2 of 7 subjects (29%) in the 400 mg group and in 2 of 12 subjects (17%) in the 300 mg group, compared to 0 of 8 pooled subjects (0%) who received placebo.

C. Euphoria-Type AEs in a Phase 1 Electrocardiographic Study (Study #SP640)

Conclusion

Oral administration of lacosamide produced a high rate of the AE "Feeling Drunk" in a Phase 1 electrocardiographic study in healthy subjects.

Study Design

Healthy subjects (n = 220) participated in a double blind, randomized, parallel design study evaluating the electrocardiographic effects (including QTc response) following oral administration of lacosamide (400 and 800 mg/day), moxifloxacin (400 mg/day) or placebo for up to 6 days. Moxifloxacin was included as the positive control drug because of its known ability to prolong QTc interval.

Adverse Events Related to Abuse Potential

The euphoria-type AE "Feeling Drunk" was reported in 11 of 71 subjects (16%) who received the 800 mg dose of lacosamide, in 5 of 60 subjects (8%) who received the 400 mg dose of lacosamide, in 2 of 62 subjects (3%) who received placebo and 0 of 54 subjects (0%) who received the moxifloxacin.

D. Euphoria-Type AEs in Phase 2/3 Clinical Efficacy Studies

Conclusion

A low incidence of euphoria-type AEs were reported in double blind and open label Phase 2/3 clinical efficacy studies (Study # SP586, SP598, SP607, SP614, SP615, SP 665, SP667, SP742, SP743, SP745, SP746, SP754, SP755, SP756, SP768, SP774, SP830) with lacosamide in partial onset seizure patients and in diabetic neuropathic pain patients, compared to patients treated with placebo. The data from these clinical efficacy trials are difficult to interpret in terms of their direct relationship to lacosamide, however, given that patients with both conditions were maintained on a variety of other medications, including those with known abuse potential or with known ability to produce psychiatric or neurological AEs.

Overview of Phase 2/3 Clinical Efficacy Studies

Lacosamide has been tested in clinical efficacy trials for the indications of diabetic neuropathic pain and epilepsy. Doses tested for both indications include 200, 400 and 600 mg/day (p.o.), with dose run-up phases included in each treatment study.

Incidence of Euphoria-Type AEs and Hallucination

The incidence of euphoria-type AEs (including euphoric mood, elevated mood, feeling drunk, feeling abnormal) and hallucination in Phase 2/3 clinical efficacy trials in patients treated with lacosamide was evaluated in comparison to patients treated with placebo.

In the partial-onset seizure patient population, euphoria-type AEs were reported in 16 of 944 patients (1.7%) participating in double-blind, placebo-controlled trials who received lacosamide at doses ranging from 100-600 mg/day (Study # SP667, SP754, SP755). In contrast, a euphoria-type AE was reported in 1 of 364 patients (0.2%) who received placebo in the same trials. Five of the 16 patients who experienced a euphoria-type AE during lacosamide treatment reported two incidents of the AE during the trial. In the same trials, hallucination was reported in 4 of 944 patients (0.4%) receiving lacosamide at doses ranging from 100-600 mg/day. None of these individuals reported more than one incident of the AE. In placebo-treated patients, hallucination was reported in 1 of 364 patients (0.2%).

The incidence of euphoria-type AEs in the partial-seizure patient population was also evaluated with the inclusion of patient data from the open-label trials (Study # SP586, SP598, SP607, SP615, SP756, SP774). Some patients previously treated with lacosamide or placebo continued in the open-label phase study while being treated with lacosamide at doses ranging from 100-600 mg/day. However, the open-label phase data are not separable from the double-blind, placebo-controlled phase data because of the data presentation method used by the Sponsor. When the double-blind, placebo-controlled data and the open-label data are assessed together, 34 patients out of a total of 1327 patients (2.6%) who participated in either phase of the study experienced euphoria-type

AEs after receiving lacosamide at a dose ranging from 100-600 mg/day. This rate is slightly higher than the 1.7% reported in the double-blind phase of the study. Similarly, when the two phases of the study are evaluated for hallucinations, this AE was reported by 18 patients out of a total of 1327 patients (1.4%). This rate is also slightly higher than the 0.4% reported in the double-blind phase of the study.

In the diabetic neuropathic pain patient population, euphoria-type AEs were reported in 9 of 1023 patients (0.9%) participating in double-blind, placebo-controlled trials who received lacosamide at doses ranging from 100-600 mg/day (Study # 614, 742, 743, 768). In contrast, a euphoria-type AE was reported in 1 of 292 patients (0.3%) who received placebo in the same trials. No patients reported more than one euphoria-type AE during the trial. In the same patient population, hallucination was reported in 1 of 1023 patients (0.1%) receiving lacosamide at doses ranging from 100-600 mg/day. Hallucination was not reported in placebo-treated patients.

An open-label phase was also included in the study design where diabetic neuropathic pain patients previously treated with lacosamide or placebo could continue in the study while being treated with lacosamide (Study # 665, 745, 746, 830). When the open-label data are evaluated, there is only one additional euphoria-type AE reported. As with the partial-seizure patient studies, the open-label data are not separable from the double-blind, placebo-controlled data. When the double-blind, placebo-controlled data and the open-label data are assessed together, 10 patients out of a total of 1566 patients (0.6%) who participated in either phase of the study experienced euphoria-type AEs after receiving lacosamide at a dose ranging from 100-600 mg/day. This rate is slightly lower than the 0.9% reported in the double-blind phase of the study. An additional two patients participating in the open-label phase of the trial reported hallucination, for a total of 3 of 1566 patients (0.2%) participating in the double-blind, placebo-controlled phase and the open-label phase of the study. This is slightly higher than the 0.1% rate of hallucination reported in the double-blind phase of the study.

E. Evaluation of Physical Dependence in a Phase 2/3 Clinical Efficacy Study (Study # SP746)

Conclusion

No signs or symptoms indicative of a withdrawal syndrome were observed that are indicative of the presence of physical dependence.

Study Design

A prospective evaluation of physical dependence was conducted in 106 diabetic neuropathic pain patients who had been treated with lacosamide at doses of 200 and 400 mg/day (p.o.) for at least one year and then abruptly discontinued from lacosamide.

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Results

Few AEs were observed during the 4-week discontinuation period, with the exception of re-emergence of disease symptoms.

II. Summary of Data Related to Abuse Potential from Preclinical Studies

A. Receptor Binding Studies (Study 817003, 817004, 6065, 10263)

Conclusion

The binding data demonstrate that lacosamide and its major metabolite SPM-12809 (O-desmethyl-lacosamide) do not have a receptor binding profile that is similar to any known drugs of abuse. These two compounds do not bind significantly to any major or minor neurotransmitter system in the brain with the exception of the sodium channel and CRMP-2. Neither of these mechanisms have been previously associated with abuse potential.

Receptor Binding Study with Lacosamide

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A comprehensive study of more than 100 binding sites was conducted with lacosamide. Lacosamide is [redacted] D-serine, which is known to bind at the glycine site of the NMDA receptor-channel complex. However, lacosamide showed no affinity for the glycine site. Additional analysis of binding sites typically associated with abuse potential (dopamine, serotonin, GABA, opioid, cannabinoid and monoamine transporters) did not show significant affinity.

Lacosamide was shown to only have affinity for two sites: the sodium channel and the collapsin response mediator protein 2 (CRMP-2). The effect of lacosamide on the sodium channel appears to produce enhancement of sodium channel slow inactivation without effects on fast inactivation. CRMP-2 is a protein associated with developmental processes in the CNS including those induced by brain derived neurotrophic factor (BDNF). It is unclear at this time how lacosamide interacts with CRMP-2.

Receptor Binding Study with SPM-12809, the Major Metabolite of Lacosamide

The pharmacokinetic report notes that there is one major metabolite of lacosamide in rodents, dogs and humans: SPM-12809 (O-desmethyl-lacosamide). Identical binding experiments as described above were conducted with SPM-12809, but no significant binding was seen for any of 100 sites tested.

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B. Preclinical Behavioral Studies

Preclinical behavioral studies conducted with lacosamide include general behavioral observations, self-administration, conditioned place preference, drug discrimination and physical dependence.

Pharmacokinetic data show that a 30 mg/kg oral dose of lacosamide in rats produces Cmax and AUC values that are comparable to those produced in humans following an oral dose of 600 mg/day [redacted]

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General Behavioral Responses to Lacosamide (Study #20000379)

Conclusion

These tests show that lacosamide produces a sedative behavioral profile in rats.

Study Design and Results

In the Irwin test of general behavioral responses, lacosamide dose-dependently produced sedative-type behaviors in rats, including sedation, rolling gate, decreased muscle tone, decreases in spontaneous locomotion, passivity to finger approach and ataxia. Other behaviors observed included hypothermia, decreased respiration, and Straub tail. Rats received lacosamide by two routes: oral (8, 16, 32, 64, 128 and 256 mg/kg) and intraperitoneal (4, 8, 16, 32, 64 and 128 mg/kg). The range of oral doses produces pharmacokinetics (Cmax and AUC) that are equivalent to one-quarter up to 8.5 times greater than those produced by [redacted] (600 mg/day, p.o.). For the intraperitoneal route of administration, the 32 mg/kg dose produces AUC values that are slightly greater than those produced by the [redacted] so it is likely that the AUC values in rats range from 1/10 to 4 times greater than those produced by the 600 mg/day human oral dose.

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Additionally, rats were tested in the rotorod test of muscle control and coordination at doses of 32, 64 and 128 mg/kg (p.o.) and 8, 16, and 32 mg/kg (i.p.). At the highest oral dose in rats (equivalent to 4 times the [redacted] dose in humans), there was a significant reduction in performance by rats on the rotorod test. Similarly, there was a significant reduction in performance at the highest intraperitoneal dose, which is equivalent to the highest proposed human therapeutic dose.

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Drug discrimination (Study #05.237/5)

Conclusion

The majority of the rats that were trained to discriminate lacosamide identified a variety of depressant drugs with known abuse potential (a barbiturate, a benzodiazepine and an

opioid) as similar to lacosamide. These data demonstrate that lacosamide may have abuse potential.

Study Design

Rats (n = 11) were trained to discriminate lacosamide (10 mg/kg, i.p.) from saline under an FR10 schedule of reinforcement. This dose produces an AUC value that is 1/3 of that produced by [redacted] lacosamide (600 mg/day, p.o.). Given the linear pharmacokinetics of lacosamide, it is likely that the 10 mg/kg (i.p.) dose in rats produces AUC values that are similar to those produced by the lowest proposed human therapeutic dose (200 mg/day, p.o.).

Challenge sessions with lacosamide (0.3, 1.0, 3.0, 10 mg/kg, i.p.), alprazolam (0.5, 1.0, 2.0 mg/kg, i.p.), morphine (0.5, 1.0, 2.0, 4.0 mg/kg, i.p.), phencyclidine (0.5, 1.0, 2.0 mg/kg, i.p.) and phenobarbital (4.0, 8.0, 16.0 mg/kg, i.p.) were conducted to determine generalization to the lacosamide interoceptive cue. Doses chosen for these comparator drugs are justified on the basis of historical use in published scientific studies.

Results

In drug discrimination studies, animals must select the training drug-appropriate lever at least 80% in order for the test drug to be considered to have full generalization to the training drug. In the present study, the only test condition that produced full generalization to the lacosamide training cue was lacosamide itself at 10 mg/kg (the same dose as that used in the training condition) with drug-lever responding at 81%.

After data from all animals were averaged, partial generalization above 50% was seen with the following treatments: phenobarbital 8.0 mg/kg (74%), alprazolam 1.0 mg/kg (69%), alprazolam 2.0 mg/kg (61%), morphine 1.0 mg/kg (60%), and morphine 2.0 mg/kg (54%). However, this partial generalization typically represented responding in which a large proportion of the animals responded almost exclusively on the drug lever, while the others responded most of the time on the saline lever. A low response rate often accompanied saline-associated responses.

Self-Administration (Study # 05.673/4)

Conclusion

Lacosamide does not produce self-administration in rats that were trained to self-administer cocaine.

Study Design

Rats (n = 9) were trained to self-administer cocaine (0.32 mg/kg/infusion, i.v.) under an FR2 schedule of reinforcement. Cocaine is the drug typically used in self-administration

studies for training purposes. After self-administration of cocaine was stable, rats were tested with saline to insure a low self-administration response. Once cocaine and saline trials had concluded, testing with lacosamide at doses of 1.0, 3.0 and 10.0 mg/kg/infusion (i.v.) was initiated. The highest dose of lacosamide produces an AUC value that is approximately 1/2 of that produced by the [redacted] (600 mg/day, p.o.). Given the linear pharmacokinetics of lacosamide, it is likely that the two lower doses tested are equivalent to 1/20 and 1/6 of 600 mg/day (p.o.) human dose.

During lacosamide trials, rats received a priming dose of lacosamide immediately prior to being placed in the test cage to signal what test drug that would be available during the session. Exposure to each dose of lacosamide occurred for at least 4 sessions.

Results

When lacosamide was presented as the test compound, it failed to maintain self-administration at doses of 1.0, 3.0 and 10.0 mg/kg/infusion (i.v.). However, when cocaine (0.32 mg/kg/infusion, i.v.) was reintroduced, it continued to maintain high levels of self-administration, showing that rats are responsive to a drug with rewarding properties.

Conditioned place preference (Study #05.122/6)

Conclusion

Administration of lacosamide to rats did not induce a conditioned place preference, while administration of morphine to rats did produce a conditioned place preference.

However, the results from the morphine administration are unusual for two reasons: first, the percent of time spent in the drug-paired compartment may be low for a drug with known abuse potential and second, the dose of morphine was very high. In fact, the narrative notes that the present study is a replication of an earlier study with the same design, which was conducted because the first study did not show a statistically significant difference between vehicle and morphine at 64 mg/kg (p.o.).

Thus, the ability of lacosamide to produce conditioned place preference in the laboratory that conducted this study is questionable, making the data difficult to interpret. However, these negative results are consistent with those of the self-administration study with lacosamide.

Study Design

Rats (n = 12/group) were used to investigate the ability of lacosamide to induce conditioned place preference. In this test, rats receive repeated doses of vehicle and a drug, with each treatment paired with one side of a test cage, separated from the other side by a divider barrier. Each side of the test cage presents unique environmental cues

(such as light/dark, patterned or smooth floors, etc.) so the rat can learn to associate each drug treatment response with a particular environment. After rats have been trained, they are placed in the test cage with the barrier removed to measure which side the animal prefers to spend time in. Drugs that produce rewarding effects typically induce animals to spend more time on the side with which the drug was associated.

In the present study, rats were trained to distinguish vehicle (p.o.) from three drug treatments: lacosamide at two doses (30 and 100 mg/kg, p.o.) and morphine (as the positive control; 64 mg/kg, p.o.). The 30 mg/kg dose of lacosamide produces a pharmacokinetic profile (Cmax and AUC) that is similar to that produced by the [redacted] b(4) ; (600 mg/day, p.o.)

Results

The results of the study show that vehicle produced 43% of time spent in vehicle-paired compartment and 57% of their time in the drug-paired compartment. It is unclear from the data whether this number represents a summation of all vehicle conditions from all drug trials or from one vehicle condition, given that separate vehicle data are not presented for each drug condition.

Lacosamide (30 and 100 mg/kg, p.o.) produced 54% and 58% time spent (respectively) in drug-paired compartment. This implies that on test days, rats spent 46% and 42% of their time (respectively) in the vehicle-associated side of the cage. There was no statistical significance between the two drug conditions and the vehicle conditions. This demonstrates that lacosamide does not produce a conditioned place preference.

Morphine (64 mg/kg, p.o.) produced 69% time spent in drug-paired compartment. This implies that on test days, rats spent 31% of their time on the vehicle-associated side of the cage. These results demonstrate statistical significance between the two treatment conditions, indicating that morphine produced a conditioned place preference.

C. Physical Dependence Studies in Rats and Dogs

Conclusion

No evidence of a withdrawal syndrome indicative of physical dependence was observed in rats and dogs after abrupt lacosamide discontinuation following chronic exposure in toxicity studies.

Rat Physical Dependence Study (Study # RS211)

In the rat study, male and female animals (n = 25/sex) received daily oral doses of vehicle or 30, 90 and 180 mg/kg lacosamide for 26 weeks. The 30 mg/kg dose is equivalent to

b(4)

(600 mg/day, p.o.), with the other two doses representing 3 times and 6 times (respectively) the

b(4)

Five rats in each dose/sex group were observed for 4 weeks following lacosamide discontinuation. The checklist for withdrawal-associated behaviors included the following: death, motility, unresponsiveness, prostrate, muscle tone, salivation, loss of condition of fur, excitability, sensitivity, appetite, stereotypy, writhing, head hiding, teeth chattering, wet-dog shakes, ptosis, convulsions, diarrhea, lacrimation, rhinorrhea, and piloerection.

At the two lower doses (30 and 90 mg/kg), no behavioral signs were observed during drug administration. However, most animals at the highest dose (180 mg/kg) exhibited various behavioral manifestations during the lacosamide administration period. However, none of the animals at any dose of lacosamide (5/sex/dose) that were observed during the 4-week drug discontinuation period exhibited any of the behaviors associated with withdrawal on the behavioral checklist.

Dog Physical Dependence Study (Study # RS211)

In the dog study male and female animals (n = 7/sex) received daily oral doses of vehicle, and 5, 10 and 20+25 mg/kg (20 mg/kg for first 5 weeks, 25 mg/kg for remainder of study) lacosamide for 12 months. The highest dose (20+25 mg/kg) produces a pharmacokinetic profile (Cmax and AUC) that is similar to that produced by th

b(4)

(600 mg/day, p.o.). Thus, the two lower doses represent one-quarter and one-half equivalents of the highest proposed therapeutic dose.

Two dogs in each group were observed for 4 weeks following lacosamide discontinuation. The checklist for withdrawal-associated behaviors included the following: death, prostration, ataxia, convulsions, defecation, motility, salivation, tremor, vocalization, vomiting, opisthotonus, respiration rate, excitation, loss of condition of coat, head shaking, chewing, impaired reflex, skin condition, pupil diameter, mucous membrane, swollen flews, flattened posture, thirst and urination, feces consistency, and cyclus.

At the two lower doses (5 and 10 mg/kg), no behavioral signs were observed during drug administration. However, most animals at the highest dose (20+25 mg/kg) exhibited various behavioral manifestations during the lacosamide administration period. However, none of the animals (5/sex/dose) observed during the 4-week drug discontinuation period exhibited any of the behaviors associated with withdrawal on the behavioral checklist.

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/s/

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5/9/2008 02:35:03 PM
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there are — NDAs for DNP - this is #1 b(4)

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