	12809
PK Assessment	Lacosamide and SPM 12809 in plasma Cmax, Cmax,norm and CTrough and normalized
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma:

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 (am and pm) by actual daily dose are presented in the following tables.

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 200mg/day						
30-minute						
Day 2 am predose (C_{trough} iv)	4	4	2.3563 (0.59347)	2.3650	1.700	2.995
Day 2 am postdose (C_{max} iv)	4	4	5.0813 (0.91183)	5.2250	3.895	5.980
Day 2 pm predose (C_{trough} iv)	5	5	2.6300 (1.10937)	2.5850	1.570	4.390
Day 2 pm postdose (C_{max} iv)	3	3	5.3933 (1.48359)	4.7500	4.340	7.090
15-minute						
Day 2 am predose (C_{trough} iv)	16	16	2.7538 (0.87086)	2.6625	1.650	4.600
Day 2 am postdose (C_{max} iv)	14	14	5.5186 (1.16874)	5.5400	3.870	7.380
Day 2 pm predose (C_{trough} iv)	15	15	2.6333 (0.78026)	2.5000	1.510	4.045
Day 2 pm postdose (C_{max} iv)	16	16	5.8066 (2.60599)	5.5700	2.250	14.285
10-minute						
Day 2 am predose (C_{trough} iv)	2	2	1.7925 (0.61165)	1.7925	1.360	2.225
Day 2 am postdose (C_{max} iv)	2	2	5.5225 (2.71175)	5.5225	3.605	7.440
Day 2 pm predose (C_{trough} iv)	2	2	1.6050 (0.50912)	1.6050	1.245	1.965
Day 2 pm postdose (C_{max} iv)	2	2	5.0725 (1.94808)	5.0725	3.695	6.450

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 300mg/day						
30-minute						
Day 2 am predose (C_{trough} iv)	3	3	3.1650 (0.80261)	3.1500	2.370	3.975
Day 2 am postdose (C_{max} iv)	2	2	7.3025 (0.32173)	7.3025	7.075	7.530
Day 2 pm predose (C_{trough} iv)	2	2	3.4000 (0.42426)	3.4000	3.100	3.700
Day 2 pm postdose (C_{max} iv)	2	2	6.9800 (1.11723)	6.9800	6.190	7.770
15-minute						
Day 2 am predose (C_{trough} iv)	18	18	3.6533 (0.96793)	3.3675	1.900	6.015
Day 2 am postdose (C_{max} iv)	17	17	7.7153 (1.95741)	7.1100	5.465	12.395
Day 2 pm predose (C_{trough} iv)	16	16	3.3406 (0.96508)	3.1100	1.685	5.990
Day 2 pm postdose (C_{max} iv)	15	15	7.3913 (1.72096)	7.0250	4.980	11.290
10-minute						
Day 2 am predose (C_{trough} iv)	4	4	2.7350 (0.74001)	2.8275	1.775	3.510
Day 2 am postdose (C_{max} iv)	4	4	7.6813 (1.70842)	8.4800	5.125	8.640
Day 2 pm predose (C_{trough} iv)	4	4	2.5075 (0.77327)	2.5350	1.710	3.250
Day 2 pm postdose (C_{max} iv)	4	4	6.6575 (1.61383)	6.8125	4.870	8.135

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 400mg/day						
30-minute						
Day 2 am predose (C_{trough} iv)	12	12	4.7842 (1.49153)	4.4625	2.935	7.655
Day 2 am postdose (C_{max} iv)	11	11	9.8236 (2.46334)	10.5750	5.590	13.440
Day 2 pm predose (C_{trough} iv)	11	11	4.5809 (1.51039)	4.3850	2.450	7.500
Day 2 pm postdose (C_{max} iv)	11	11	9.4273 (2.13709)	9.8350	5.245	12.570
15-minute						
Day 2 am predose (C_{trough} iv)	26	26	4.9600 (1.74908)	4.7125	2.725	10.725
Day 2 am postdose (C_{max} iv)	25	25	10.4720 (2.51337)	10.1800	7.275	18.135
Day 2 pm predose (C_{trough} iv)	26	26	4.6715 (1.43918)	4.3550	2.620	8.330
Day 2 pm postdose (C_{max} iv)	26	26	9.9687 (2.93351)	9.5075	3.990	15.565
10-minute						
Day 2 am predose (C_{trough} iv)	7	7	4.2664 (1.40990)	4.3450	2.730	6.895
Day 2 am postdose (C_{max} iv)	6	6	12.7883 (2.79038)	12.2400	9.780	16.650
Day 2 pm predose (C_{trough} iv)	7	7	3.9557 (1.79375)	3.4400	2.335	7.570
Day 2 pm postdose (C_{max} iv)	7	7	10.7521 (3.54318)	10.1450	6.900	17.130

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 500mg/day						
30-minute						
Day 2 am predose (C_{trough} iv)	5	5	9.6600 (4.33103)	9.0150	6.200	16.825
Day 2 am postdose (C_{max} iv)	5	5	16.3320 (3.31565)	17.3250	11.300	19.935
Day 2 pm predose (C_{trough} iv)	5	5	8.4830 (3.36541)	8.7350	5.170	13.590
Day 2 pm postdose (C_{max} iv)	5	5	15.0200 (3.78553)	14.8450	10.245	19.770
15-minute						
Day 2 am predose (C_{trough} iv)	8	8	6.2494 (1.65881)	5.8100	4.185	9.110
Day 2 am postdose (C_{max} iv)	8	8	11.9425 (1.65198)	11.8875	9.530	15.140
Day 2 pm predose (C_{trough} iv)	8	8	5.1869 (1.53381)	4.8125	3.305	8.535
Day 2 pm postdose (C_{max} iv)	8	8	11.3131 (2.94770)	10.6125	7.930	15.685
10-minute						
Day 2 am predose (C_{trough} iv)	4	4	6.4213 (1.94006)	6.5575	3.925	8.645
Day 2 am postdose (C_{max} iv)	4	4	14.7113 (1.63288)	14.2975	13.220	17.030
Day 2 pm predose (C_{trough} iv)	4	4	6.3563 (2.55900)	5.9350	3.805	9.750
Day 2 pm postdose (C_{max} iv)	3	3	12.0567 (1.55644)	12.2200	10.425	13.525

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 600mg/day						
30-minute						
Day 2 am predose (C_{trough} iv)	9	9	8.2706 (2.68257)	7.3750	5.800	13.390
Day 2 am postdose (C_{max} iv)	9	9	15.5678 (3.25722)	15.8450	11.115	19.785
Day 2 pm predose (C_{trough} iv)	10	10	7.2890 (2.60923)	6.1550	4.870	12.640
Day 2 pm postdose (C_{max} iv)	9	9	16.1572 (4.50029)	15.1600	10.840	24.695
15-minute						
Day 2 am predose (C_{trough} iv)	16	16	8.1778 (3.20534)	8.4450	2.910	14.865
Day 2 am postdose (C_{max} iv)	17	17	15.9347 (4.06896)	16.2350	8.365	23.085
Day 2 pm predose (C_{trough} iv)	16	16	7.6791 (2.69488)	8.1075	2.590	11.850
Day 2 pm postdose (C_{max} iv)	17	17	15.3206 (4.38386)	14.6850	8.010	23.110
10-minute						
Day 2 am predose (C_{trough} iv)	3	3	9.4600 (2.23002)	9.4500	7.235	11.695
Day 2 am postdose (C_{max} iv)	3	3	17.4617 (2.18815)	17.4000	15.305	19.680
Day 2 pm predose (C_{trough} iv)	3	3	8.7367 (1.63947)	8.9650	6.995	10.250
Day 2 pm postdose (C_{max} iv)	2	2	18.0125 (0.83792)	18.0125	17.420	18.605

Descriptive statistics for C_{trough} (predose) and C_{max} (end of infusion) LCM plasma concentration on Day 2 by actual daily dose and time point
Population: Pharmacokinetic Set

Actual daily dose/ Infusion duration/ Time point	Concentration in µg/mL					
	n	n>LOQ	Mean (SD)	Median	Min	Max
LCM 700mg/day[a]						
15-minute						
Day 2 am predose (C_{trough} iv)	4	4	11.0025 (6.98277)	8.1375	6.340	21.395
Day 2 am postdose (C_{max} iv)	4	4	19.3900 (4.01535)	18.8000	15.200	24.760
Day 2 pm predose (C_{trough} iv)	4	4	10.5188 (6.53178)	8.2775	5.420	20.100
Day 2 pm postdose (C_{max} iv)	4	4	17.6463 (4.14554)	16.8575	13.485	23.385
LCM 800mg/day[a]						
15-minute						
Day 2 am predose (C_{trough} iv)	2	2	11.5225 (3.77949)	11.5225	8.850	14.195
Day 2 am postdose (C_{max} iv)	2	2	23.0025 (6.40992)	23.0025	18.470	27.535
Day 2 pm predose (C_{trough} iv)	2	2	10.9650 (3.52139)	10.9650	8.475	13.455
Day 2 pm postdose (C_{max} iv)	2	2	22.7825 (0.17324)	22.7825	22.660	22.905

iv=intravenous; LCM=lacosamide; LOQ=limit of quantification; Min=minimum; Max=maximum; n>LOQ=the number of subjects with plasma levels above the LOQ (0.05µg/mL); SD=standard deviation
a There were no subjects in the 30- and 10-minute infusion duration groups who took LCM 700mg/day or LCM 800mg/day.

These Tables show that Lacosamide plasma concentrations (C_{trough}, C_{max}) were similar across all infusion duration (10, 15 and 30 minutes) groups within the daily dose groups of LCM 200mg/day-600mg/day. Only subjects in the 15-minute infusion duration group received LCM 700mg/day-800mg/day. The LCM plasma concentrations (C_{trough}, C_{max}) increased proportionately as the actual daily dose increased.

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

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

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

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

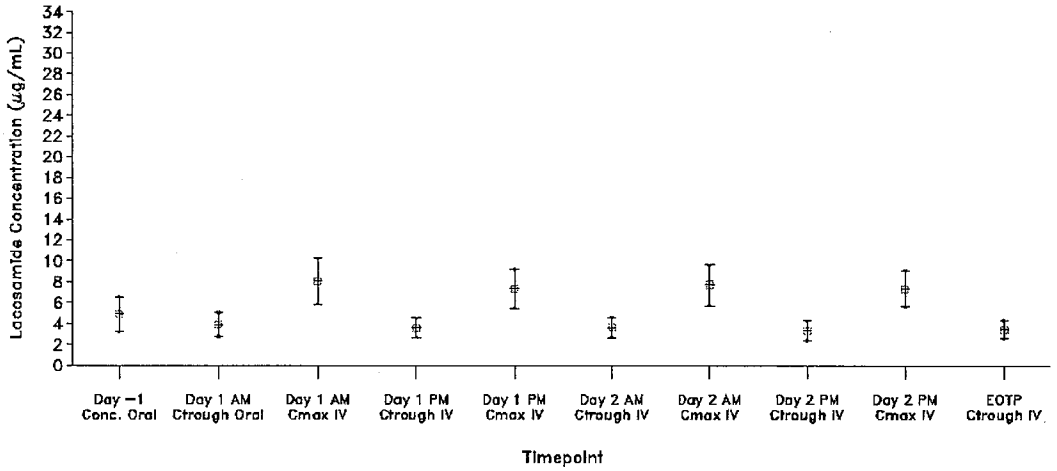
a Only subjects with a valid Day 1 am predose plasma value and a valid predose value for Day 1 pm, Day 2 am, and Day 2 pm were included.

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

Lacosamide plasma concentration (mean ±SD) versus time point for a 15 minute infusion at the 300 mg/day dose is given below, showing similar Cmax and C_{trough} between oral and iv LCM . Similar plots of different infusion groups and doses were available.

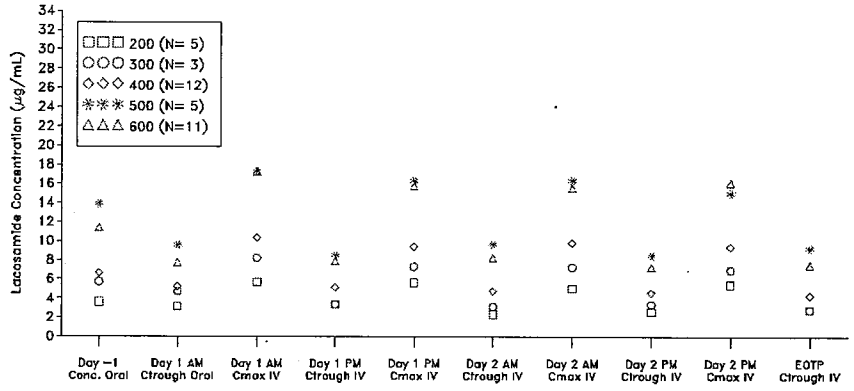
Figure 1.7

Lacosamide Concentration (mean±SD) versus Timepoint by Infusion Duration and Actual Daily Dose
Infusion Duration: 15-minute
Actual Daily Dose: 300mg/day (N=18)

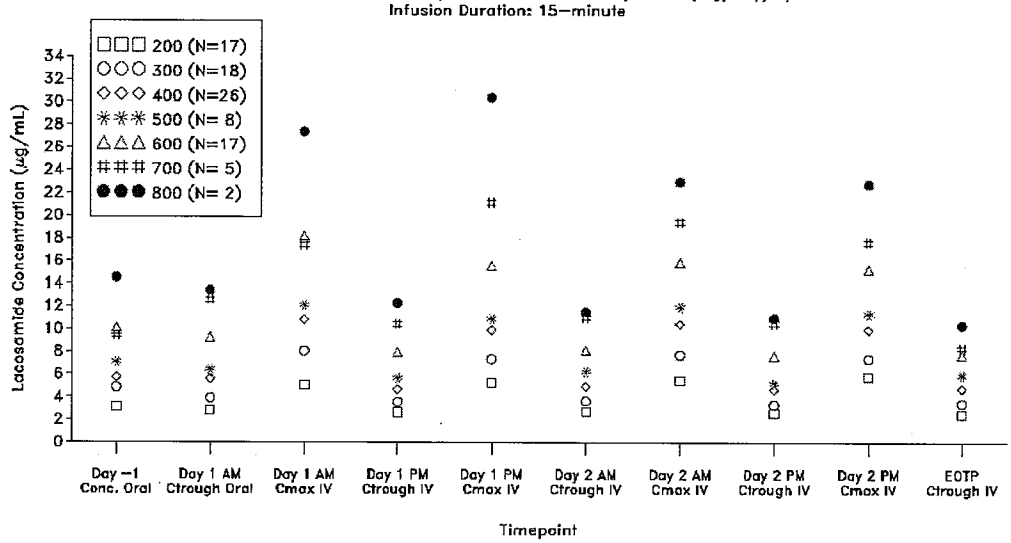


Plasma concentrations for all doses by infusion duration is shown in the following Figures:

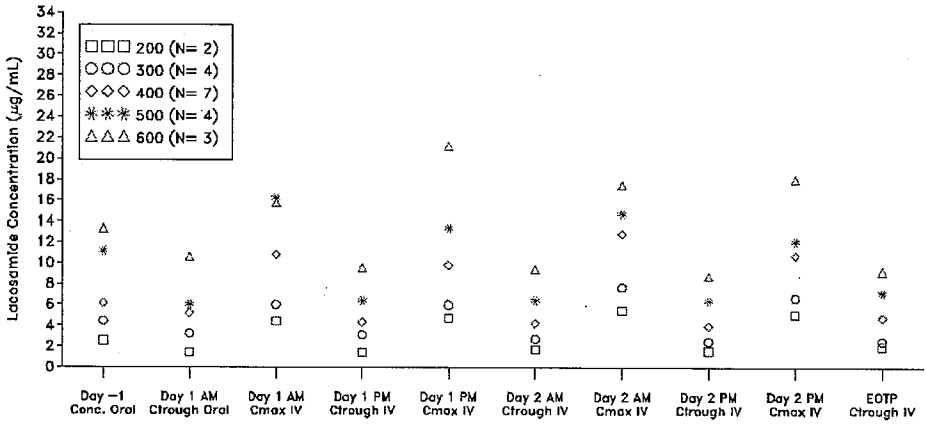
Mean Lacosamide Concentration versus Timepoint for all Actual Daily Doses (mg/day) by Infusion Duration
Infusion Duration: 30-minute



Mean Lacosamide Concentration versus Timepoint for all Actual Daily Doses (mg/day) by Infusion Duration
Infusion Duration: 15-minute



Mean Lacosamide Concentration versus Timepoint for all Actual Daily Doses (mg/day) by Infusion Duration
Infusion Duration: 10-minute



The above figures also show that C_{max}'s of a given dose are comparable across all infusion groups, as can be also seen from the mean data given in the previous Tables.

The plasma concentration (C_{trough}, C_{max}) of SPM 12809 was similar across all infusions durations within the daily dose groups of LCM. The sponsor did not give summary Tables for the metabolite concentrations, but the individual Tables were reviewed. The concentrations of concomitant AEDs was also similar across all infusion groups.

Sponsor's conclusion on safety (to be reviewed by MO as well):

There were relatively few treatment-emergent AEs reported during the trial. In the 30-, 15-, and 10-minute infusion duration groups, 43%, 24%, and 35% of subjects, respectively, reported at least 1 treatment-emergent AE during the Treatment Phase. The frequency of AEs did not increase with more days of exposure nor with shorter infusion durations.

Conclusions:

In general plasma concentrations were similar between the oral and iv dosing and across all infusion groups, although the number of subjects in some of the dose and infusion groups are small.

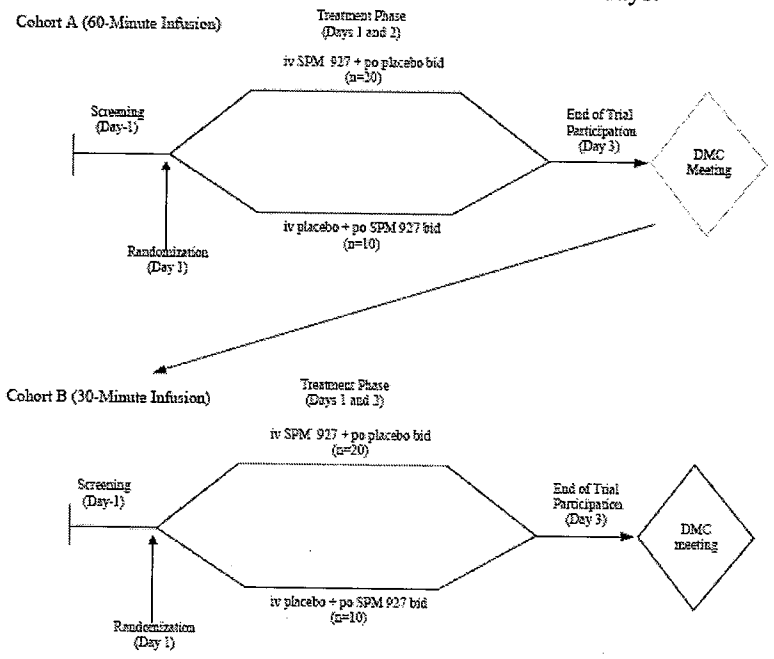
Study SP616: A multicenter, double-blind, double-dummy, randomized trial to investigate the safety, tolerability and pharmacokinetics of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization

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

Objectives:

The objectives of this trial were to evaluate the safety, tolerability, and pharmacokinetics of SPM 927 when given as iv infusions compared with oral administration of the same dose strengths in subjects who were receiving oral SPM 927 in addition to 1 or 2 concomitant antiepileptic drugs (AEDs) for partial seizures with or without secondary generalization.

The study design is as follows:

Trial Site	Seven (7) trial sites in the United States of America (USA) and Lithuania
Study Design	This was a multicenter, double-blind, double-dummy, randomized trial. A total of 60 subjects, who were participating in an open-label extension trial (SP615) of oral SPM 927, were enrolled. Subject had been on a stable dose of LCM and concomitant AED for at least 2 weeks. The subjects were randomized in a 2:1 ratio to iv SPM 927 plus placebo tablets twice daily (bid) or iv placebo plus oral SPM 927 bid, respectively. Subjects were enrolled into 1 of 2 cohorts (A and B). The maximum duration of treatment in this trial was 3 days. 
Study Population	N=60 patients

	Age: 19-61 years (mean 41.7 years) Weight: 46.1-148.3 kg (mean 80.26 kg) Gender: 25 male and 35 females Race: 53 White, 6 Black, 1 Asian
Treatment Group	Cohort A= 60 min infusion: N=30 CohortB=30 minute infusion: N=30

Dosage and Administration	On Day -1, oral SPM 927 tablets were administered in accordance with each subject's SPM 927 dosage regimen in the open-label extension (SP615). A single infusion of iv placebo was administered in a single-blind fashion after admission procedures and screening assessments had been completed. During the Treatment Phase (Days 1 and 2), blinded trial medication (iv solution and oral tablets) was administered twice daily at 12-hour intervals, once in the morning and once in the evening. The oral trial medication was taken immediately prior to the start of iv infusion, with approximately 240mL (8 ounces) of water. On Day 3, oral SPM 927 tablet(s) were administered in the morning in accordance with each subject's SPM 927 dosage regimen in the open-label extension (SP615). The tablet(s) were administered 12 hours after the start of the evening infusion on Day 2. The tablet(s) were taken with approximately 240mL (8 ounces) of water. The dose of SPM 927 (100 to 300mg bid) was the same as the subject's current daily dose in the open-label extension trial of oral SPM 927. End of Trial Phase assessments were performed the day after the Treatment Phase was completed, after which subjects continued in the open-label extension trial (SP615). <u>Dietary regimen</u> Throughout the trial, non-alcoholic and non-caffeinated beverages and non-quinine or nongrapefruit-containing beverages were served. The subjects were not allowed to consume alcohol during the trial. Breakfast, lunch, snacks, and evening meals were served under standardized conditions. IV formulation 10 mg/ml solution (200 mg in 20 ml saline): batch WE12805 Oral formulation: 50 and 100 mg tablets: batch: 231100 (50mg SPM 927), 232010 (100mg SPM 927), and 231960 (placebo)
Sampling: Blood	<u>Blood samples For LCM:</u> Day -1: Pre-dose. Day 1: Pre-dose Day 2: Pre-dose and 0.5, 1, 1.5, 2, 4, 8, and 12 hours after the start of morning infusion of trial medication (8 samples per subject). Day 3: Pre-dose, before administration of oral SPM 927. <u>Blood sample for concomitant AED:</u> Day -1, 1, 2 and 3: predose
Urine	<u>none</u>
Feces	none
Analysis	Method: LC/MS/MS method in plasma Lower Limits of Quantitation: <u>Plasma</u>

	Lacosamide 10 ng/mL Plasma: Linear Range in plasma 10-10,000 ng /ml Quality control concentrations : 20, 500 and 4000 ng /ml Inter-day precision: < 3.4%CV for LCM Inter-day accuracy: -101.3-101.6-101.9 for LCM
PK Assessment	Lacosamide in plasma AUC(0-12), Cmax, Cmin, t1/2, normalized parameter ((parameter*Body weight[kg]/dose[mg])
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma:

In total, 8 out of 60 subjects had invalid plasma concentration data due to reasons explained in the report. No PK parameters were calculated for n=7 of these subjects. As a result, the PK Set includes n=53 subjects out of n=60 subjects with concentration data.

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

Pharmacokinetic parameters AUC(0-12), C_{max}, C_{min}, and $t_{1/2}$ were derived from concentration data of Day 2. For body weight- and dose-normalized AUC(0-12), C_{max}, and C_{min}, treatment ratios were calculated to compare the pharmacokinetics of SPM 927 after iv infusion over 60 and 30 minutes with the pharmacokinetics of SPM 927 after oral treatment within each cohort as shown in the table below.

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

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

CI= confidence interval; iv = intravenous; PBO = placebo; SD = standard deviation

Cohort A: 60-minute iv infusion; Cohort B: 30-minute iv infusion

The bioavailability of SPM 927 after iv treatment for both the 60- (Cohort A) and the 30-minute infusion (Cohort B) was comparable to that after oral treatment. Ratios iv/oral for $AUC(0\text{-}12)_{norm}$ were 95-100%, although the 90% confidence intervals were outside the acceptable range.

Values of $C_{max,norm}$ were slightly elevated after iv treatment compared to oral treatment. This is reflected in ratios iv/oral of 111-118% for $C_{max,norm}$.

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

The t_{max} was shorter after iv administration of SPM 927 compared to oral administration. Thirteen out of 17 subjects receiving the 60-minute iv infusion reached t_{max} after 60-90 minutes and 13 out of 15 subjects receiving the 30-minute iv infusion reached t_{max} after30 minutes as expected. After oral administration of SPM 927, t_{max} was reached between 1.5 and 4 hours after administration in the majority of subjects.

From predose samples on Days 1, 2 and 3, trough plasma concentrations of SPM 927 were determined. Predose concentrations on Days 2 and 3 (=trough levels after iv or oral administration of SPM 927 on Days 1 and 2 [evening dose]) were compared with predose concentrations on Day 1 (=trough level after oral SPM 927) as shown in the table below.

Comparison of trough plasma concentrations of SPM 927

Parameter (unit)	Cohort	Treatment	N	Ratio (%)	
				Day 2/Day 1	Day 3/Day 1
C_{trough} (µg/mL)	A	Oral SPM 927 / iv PBO	10	111.0	106.8
		iv SPM 927 / oral PBO	17	92.5	94.6
	B	Oral SPM 927 / iv PBO	11	119.1	124.3
		iv SPM 927 / oral PBO	15	90.6	89.2

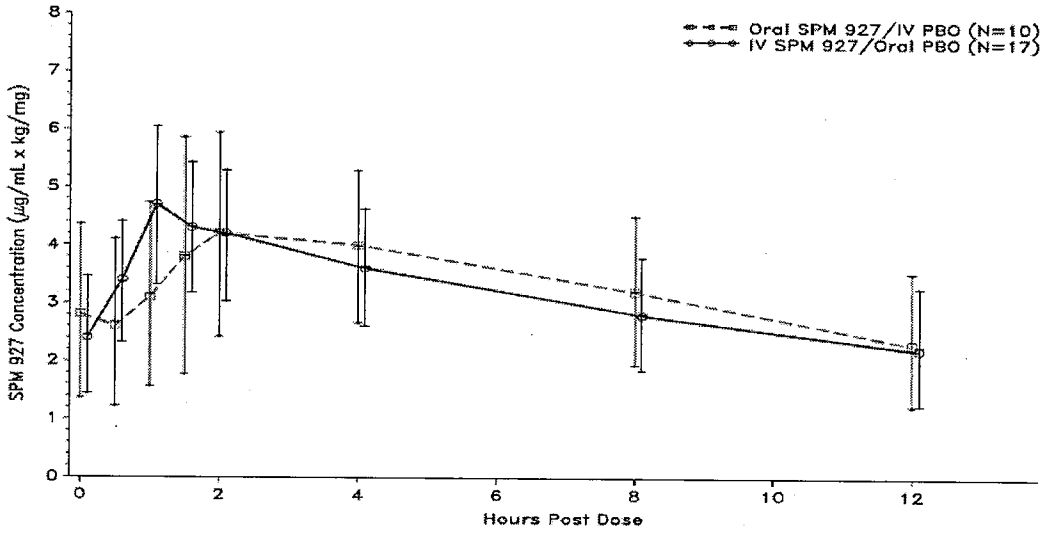
iv = intravenous; PBO = placebo
Cohort A: 60-minute iv infusion; Cohort B: 30-minute iv infusion

In subjects who received iv treatment on Days 1 and 2, mean values of C_{trough} on Days 2 and 3 (=trough levels after iv SPM 927) were slightly lower compared with Day 1 (=trough level after oral SPM 927).

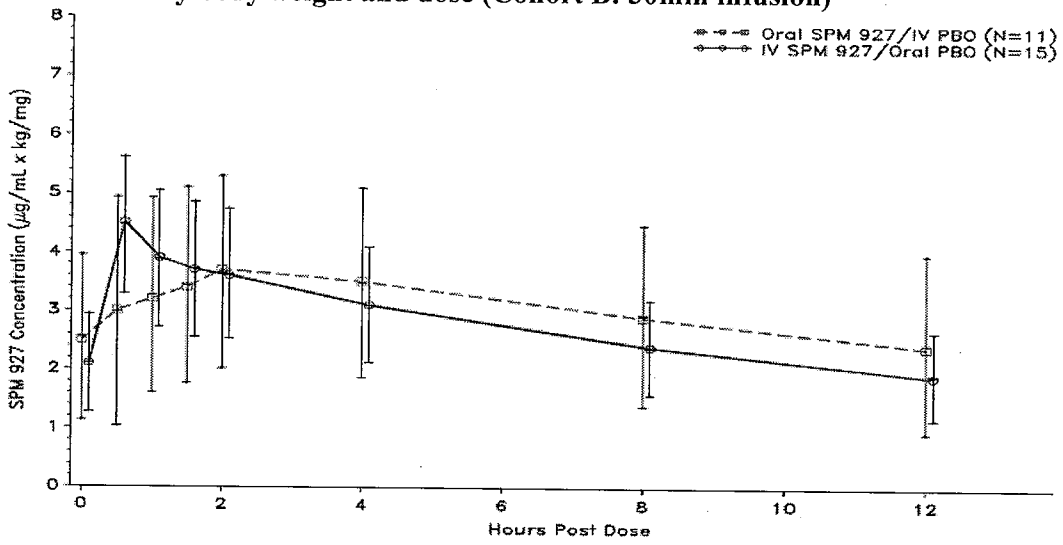
In subjects continuing with oral SPM 927 on Days 1 and 2, mean values of C_{trough} on Days 2 and 3 may were slightly increased compared to Day 1. The increase was more pronounced for subjects receiving oral SPM 927 in Cohort B.

Mean normalized SPM 927 plasma concentrations over time on Day 2 are graphically displayed below for Cohort A (60-minute iv infusion) and B (30-minute iv infusion), respectively.

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



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



As seen in the figures above, maximum mean normalized plasma concentrations of SPM 927 were higher and were reached earlier when SPM 927 was administered intravenously compared with oral administration. Maximum mean normalized plasma concentrations were reached at 30min after the 30-minute infusion, at 60min after the 60-minute infusion, and at 2 hours after oral administration. Mean plasma concentrations of SPM 927 after 4, 8, and 12 hours were slightly higher after oral SPM 927 compared with iv SPM 927.

Effect of intravenous administration of SPM 927 on concomitant antiepileptic drugs

Plasma concentrations of concomitant AEDs were determined on Day -1, Day 1, Day 2, and Day 3 simultaneously with the SPM 927 trough concentrations. For the most common concomitant AEDs, predose AED concentrations on Days 2 and 3 were compared with predose AED concentrations on Day 1 to investigate the effect of iv SPM 927 on the steady-state plasma concentrations of concomitant AEDs.

Steady state plasma concentrations of phenytoin (an inducer) and total valproic acid (an inhibitor) did not appear to be affected by administration of iv SPM 927.

In general the plasma concentrations of all the concomitant AED after iv administration were comparable to that after oral administration, but there were less than 6 subjects in each group to make any conclusions on the AED concentration with iv administration.

METABOLIC DIFFERENCES BETWEEN ORAL AND IV DOSING

Study SP643: Randomized, open-label, 2-way crossover trial to investigate the pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (CYP2C19)

Objectives:

The primary objective of this trial was to compare the pharmacokinetics and bioavailability of SPM 927 when given as intravenous solution or as oral tablet to four healthy Caucasian poor metabolizers (PM) (genotyped) compared to eight healthy Caucasian extensive metabolizers (EM).

The secondary objective was to determine the safety and tolerability of SPM 927.
The study design is as follows:

<table>
<tr><td>Trial Site</td><td>One Site in Germany</td></tr>
<tr><td>Study Design</td><td>This was an open-label, 2-way crossover trial in which healthy subjects</td></tr>
<tr><td>Study Population</td><td>N=12 Healthy subjects randomized (8 EMs and 4PMs) and N=11 valid for PK analysis
Age: EM: 26-42 years (mean 34.3years)
PM: 25-44 years (mean 34.5years)
Gender: All males
Weight: EM: 58.2-84 kg (mean 68.9 kg)
PM: 60.5-80 kg (mean 68.6 kg)
Race: All White</td></tr>
<tr><td>Treatment Group</td><td>Treatment A: IV: a single dose of 200mg SPM 927 as 50mL intravenous infusion over 60min,

Treatment B: Oral: a single dose of 200mg (2x100) SPM 927, followed by multiple doses of 200mg SPM 927 bid for 4 days, then 200mg on the last day.
<table>
<tr><th>Treatment</th><th>Description of Investigational Product</th><th>Total Dose/Treatment</th></tr>
<tr><td>A (iv dose)</td><td>200mg of SPM 927 in the morning</td><td>200mg SPM 927</td></tr>
<tr><td>B (po dose)</td><td>on Day 1: 200mg SPM 927 (morning)</td><td>200mg SPM 927</td></tr>
<tr><td>B (po dose)</td><td>on Day 4 to 7: 200mg SPM 927 (morning)
plus 200mg SPM 927 (evening)</td><td>400mg SPM 927</td></tr>
<tr><td>B (po dose)</td><td>on Day 8: 200 mg SPM 927 (morning)</td><td>200mg SPM 927</td></tr>
</table></td></tr>
<tr><td>Dosage and Administration</td><td>Vials containing 200mg SPM 927, administered as intravenous infusion (50mL over 60 minutes), batch number: WE12206 (Treatment A: 040702);

Film-coated-tablets containing 100mg SPM 927, batch number: 223770 (Treatment B: 050702).</td></tr>
</table>

	Washout: Wash-Out Phase of at least 6 days between treatments
Sampling: Blood	For Lacosamide and its metabolite, SPM12809: Treatment A (iv treatment): Predose and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72 hours post administration Treatment B (oral treatment): Day 1 to 4: Predose and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72 hours post administration Day 6 and 7: Before morning and evening dose Day 8 to 11: Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours post administration
Urine	Day 1 and Day 8: at 0 hours (predose voiding), 0-12 hours, and 12-24 hours after respective dose.
Feces	none
Analysis	Method: LC/MS/MS method in plasma and urine Lower Limits of Quantitation: Plasma / Urine Lacosamide 100 ng/ml 5µg/ml SPM 12809 20 ng/ml 1µg/ml Plasma: Linear Range: 100-20,000 ng/ml in plasma for lacosamide and 20-4000 ng/ml for SPM 12809 Quality control concentrations 300, 1500, 15000 ng/ml for LCM and 60, 300 and 3000 ng/ml for SPM12809 Inter-day precision: <7.7 %CV for LCM and <9.1 for SPM12809 Inter-day accuracy: -5.1to -7.0 % bias for LCM and 5.3 to 7.3% for SPM12809 Urine: Linear Range: 5-500 µg/ml urine for lacosamide and 1-100 µg/ml for SPM 12809 Quality control concentrations 15, 40, 400 µg/ml for LCM, 3,8, 80 µg/ml for SPM12809 Inter-day precision: <7.8 %CV for LCM and <10 for SPM12809 Inter-day accuracy: -3.1 to -8.8 % bias for LCM and -13.8 to 7.5% for SPM12809
PK Assessment	Lacosamide and SPM 12809 in plasma Primary PK parameters were: • AUC(0-tz), F, Cmax t1/2 of lacosamide in plasma after SD;

	Cmax,ss, and T1/2 at steady state Secondary PK parameters were: • AUC(0-∞), AUC (0-12),t1/2, tmax of lacosamide and M1
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Method of genotyping:

For the genotyping, ethylene diamine tetraacetic acid (EDTA) blood samples were collected and DNA was isolated using standard methods according to Miller et al (Nucleic Acids Res. 1988 Feb 11;16(3):1215).
Cytochrome P450 subgroup CYP2C19 determination was done using polymerase chain reaction and restriction analysis according to Sachse et al (Am J Hum Genet. Feb;60(2):284-95, 1997).

For CYP2C19 (subfamily IIC [mephenytoin-4-hydroxilase] polypeptide 19; human genome gene locus: 10q24.1-q24.3; MIM [Mendelian inheritance in man] no. 124020), the wild-type allele and 1 mutated allele weredetermined. This covers 98% of alleles in the German population.

Allele	Type of allele	Name of allele
wt	wild type (wt)	*1
m1	Mutation (mut1)	*2

The following 3 genotypes were defined:

Phenotype	Frequency[a]	Number of active alleles	Genotype
Extensive metabolizer	64%	2	(wt + wt)
Intermediate metabolizer (heterozygous)	32%	1	(wt + mut)
Poor metabolizer	4%	0	(mut + mut)

a Phenotype frequencies are based on previous determinations of the alleles in the German population and represent expected frequencies. The frequency distribution can be different in other populations (eg, Blacks, Scandinavians).

Genotyping identified 4 homozygous poor metabolizers (2 mutated alleles).
The subjects included as extensive metabolizers were either heterozygous for the respective alleles (wild-type + mutated alleles) or homozygous (wild-type + wild-type alleles).

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma:

The summary of pharmacokinetic parameters (ranges) in the poor and extensive metabolizers are shown in the following Table:

Pharmacokinetic parameters of LCM after administration of 200mg LCM as single dose as well as after dosing at steady state in poor and extensive metabolizers (CYP2C19)

Parameter (unit)	Statistic	Poor metabolizers (N=3)		Extensive metabolizers (N=8)	
		iv	oral	iv	oral
Single dose					
$AUC_{(0-tz)}$ (µg/mL*h)	Geometric mean (CV%)	101.7 (4.7)	106.6 (3.3)	95.84 (14.9)	96.87 (19.2)
$AUC_{(0-\infty)}$ (µg/mL*h)		105.8 (5.4)	110.4 (5.1)	98.58 (14.9)	100.0 (19.4)
C_{max} (µg/mL)		5.604 (16.2)	6.882 (14.2)	5.720 (8.6)	6.209 (32.4)
$t_{1/2}$ (h)		15.04 (6.3)	14.40 (14.2)	13.63 (9.1)	13.78 (9.8)
F (%)		NA	104.4 (4.4)	NA	101.4 (7.2)
A_e (mg)		61.87 (1.4)	56.28 (24.7)	46.38 (9.1)	45.33 (18.2)
Steady state					
$AUC_{\tau,ss}$ (µg/mL*h)	Geometric mean (CV%)	NA	98.68 (3.6)	NA	94.64 (15.5)
$C_{max,ss}$ (µg/mL)		NA	12.94 (7.6)	NA	12.51 (15.2)
$t_{1/2}$ (h)		NA	16.06 (5.0)	NA	14.26 (11.0)
A_e (mg)		NA	110.5 (18.5)	NA	79.00 (19.6)

CV=coefficient of variation; F=absolute bioavailability; LCM=lacosamide; NA=not applicable

For iv – Day 1, po - Day 1, and po – Day 8, t1/2 was marginally longer in PM accompanied by a slightly higher AUC. The difference however is very small (about 10 % or lower) and unlikely of clinical relevance.

The AUCs were marginally higher after oral administration than after iv administration.

The amounts of lacosamide excreted in the urine was higher (24-34% in the iv and oral groups) in the PMs compared to the EMs. In PMs, 50.3 % of the dose was recovered in the urine in form of unchanged SPM 927, whereas in EMs the urinary recovery was only 39.5% of the dose.

The table also shows that the iv and oral PK parameters of SPM 927 on Day 1 were comparable.

The absolute bioavailability (oral/iv) in terms of AUC0-tz was 104.4% (90% CI 86-129%) in the PMs and 101.4% (90% CI 97-105%) in EMs. The larger confidence interval in the PMs could be due to the small sample size, hence these absolute bioavailabilities should be interpreted with caution.

Pharmacokinetics of SPM 12909

The pharmacokinetic parameters of the metabolite is summarized in the following Table:

Pharmacokinetic parameters of SPM 12809 after administration of 200mg LCM on Day 1 and at steady state in poor and extensive metabolizers (CYP2C19)

Parameter		Poor metabolizers (n=3)	Extensive metabolizers (n=8)
iv – Day 1			
AUC(0-∞)	h*µg/mL	not estimable	11.0 (7.2 – 17.2)
AUC(0-t_z)	h*µg/mL	1.92 (1.73 – 2.12)	10.0 (6.3 – 16.3)
C_{max}	µg/mL	0.077 (0.073 – 0.081)	0.267 (0.164 – 0.483)
t_{max}	h	12^{+} (6 – 24)	12^{+} (12 – 24)
$t_{1/2}$	h	not estimable	17.8 (12.7 – 27.8)
CL	mL/min	not estimable	285 (183 – 437)
Ae	mg	6.5^{x} (4.6 – 8.7)	18.5^{x} (9.9 – 33.7)
CL_R	mL/min	80.7 (63.1 – 113.1)	57.8 (47.6 – 71.1)
po– Day 1			
AUC(0-∞)	h*µg/mL	not estimable	13.0 (8.7 – 19.5, n=6)
AUC(0-t_z)	h*µg/mL	2.44 (1.93 – 3.37)	10.3 (3.8 – 18.1)
C_{max}	µg/mL	0.082 (0.062 – 0.125)	0.377 (0.165 – 1.06)
t_{max}	h	6^{+} (4 – 24)	12^{+} (0.8 – 12)
$t_{1/2}$	h	not estimable	17.3 (11.8 – 31.9, n=6)
CL/f	mL/min	not estimable	243 (161 – 363, n=6)
Ae	mg	6.4^{x} (4.1 – 10.4)	16.8^{x} (9.9 – 25.0)
CL_R	mL/min	72.0 (60.1 – 87.9)	48.4 (34.8 – 81.4)
po – Day 8			
AUC_{ss}	h*µg/mL	2.85 (2.45 – 3.77)	9.47 (4.72 – 14.18)
C_{max}	µg/mL	0.301 (0.259 – 0.386)	0.938 (0.470 - 1.38)
t_{max}	h	1.5^{+} (1.0 – 3)	4^{+} (0.5 – 6)
C_{min}	µg/mL	0.203 (0.169 – 0.275)	0.520 (0.068 – 1.05)
$t_{1/2}$	h	21.6 (16.1 – 32.4)	17.9 (13.4 – 26.3)
CL/f	mL/min	1104 (834 – 1284)	332 (222 – 667)
Ae	mg	11.8^{x} (9.9 – 13.4)	37.2^{x} (20.0 – 52.2)
CL_R	mL/min	68.6 (54.0 – 88.9)	62.2 (48.0 – 89.9)

$^{+}$: median, ^{x}: mean, geometric means listed in all other cases. Numbers in brackets are (ranges).

Although plasma concentrations of SPM 927 were found to be comparable (not more than 10% difference) between PM and EM, there were noticeable differences (75-80% difference) between PM and EM with respect to AUCs of the metabolite SPM 12809.

The ratio PM/EM of the parameters AUC(0-t,) or Ae of the main metabolite M1 is given in the tables below for iv and oral dosing.

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

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

AUC(0-tz) after oral dosing [h*µg/mL]

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

This shows that the formation of SPM12909 or M1 is less in the poor metabolizers, although the exposure to parent is comparable between the PMs and EMs. The metabolite is inactive, hence these differences may not be clinically relevant.

Reviewer's Note: The sponsor had noted a difference of -8.1% for M1, which was not correct.

At steady-state total urinary recovery (arithmetic means) is compared in PM and EM in the following Table after oral dosing:

Urinary recovery

	PM (n=3)	**EM (n=8)**	**difference PM-EM**
SPM 927	50.3%	39.5%	+10.8%
M_1	6.3%	19.7%	-13.4%
Total	56.5%	59.2%	- 2.7%

This again shows that the urinary recovery or the amount of metabolite excreted in the urine is much lower in the PMs after oral dosing.

Taking both observations together, this also indicates that metabolism from SPM 927 to SPM 12809 accounts only for a small part of the total elimination.

Conclusions:

- The absolute bioavailability of SPM 927 was approximately 100% in both populations (PM and EM of CYP 2C19) when administered orally.

- The plasma exposure of unchanged SPM 927 are similar in PM and EM. Marginal differences (about 10% or lower) found in pharmacokinetic parameters Cmax and Cmin of unchanged SPM 927 may be considered of minimal clinical relevance.

- After oral dosing at steady state, the amount of parent excreted in the urine after oral dosing is about 20% higher in the PMs as compared to the EMs, but the amount of metabolite excreted in the EMs is 3 fold lower in the PMs as compared to EMs. Similar trends were seen after single iv doses as well.

- Plasma concentrations of the main metabolite SPM 12809 in EM are only about 10% of those of the parent compound SPM 927. In PM the SPM 12809 plasma levels are only about 3% of SPM 927 levels. The metabolite is not active, hence these differences may not be clinically relevant.

- For both, PM and EM respectively, at steady state about 50 and 39% of the dose is recovered in the urine within a dosing interval after oral dosing as unchanged SPM 927 and SPM 12809.

- Similar exposures were seen of the parent and M1 after iv and oral dosing, suggesting similar involvement in terms of role of CYP2C19 in metabolism of lacosamide.

- As the pharmacokinetics of SPM 927, administered as tablet or as intravenous infusion, shows only small differences between PM and EM, but the metabolite shows larger differences, therefore the extent of CYP 2C19 pathway on the metabolic fate of SPM 927 is unclear. It appear that other pathways are involved in the metabolism as well, which the sponsor has not explored.

OTHER

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

Objectives:

The primary objective of this trial was to evaluate the safety and tolerability of single ascending IV doses. This study was not conducted with the to-be-marketed formulation.

The study design is as follows: b(4)

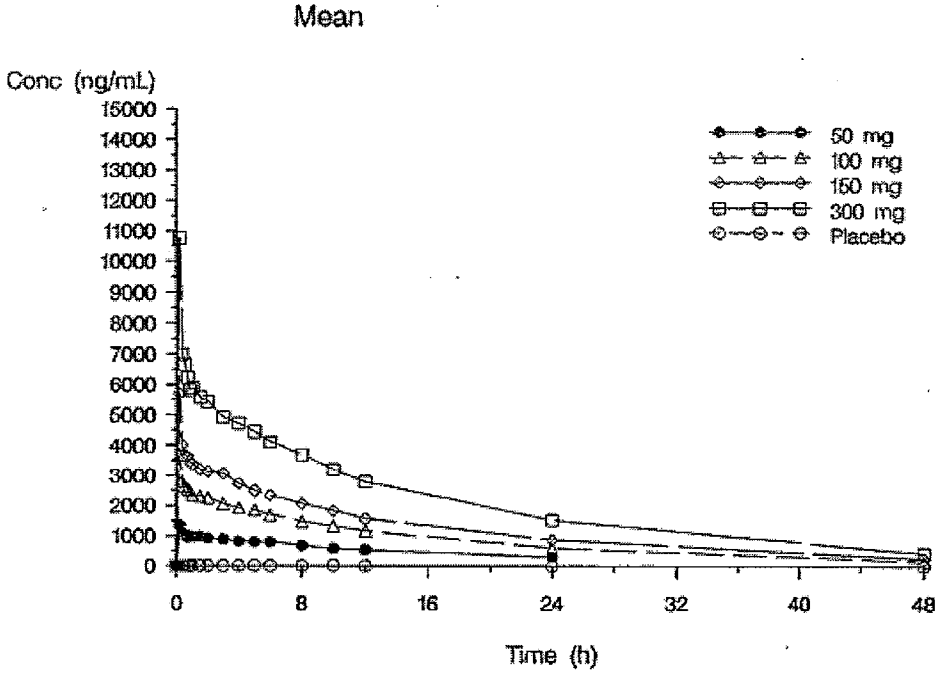
Trial Site	[redacted]
Study Design	A double blind, randomized, placebo controlled, single ascending dose clinical trial to investigate the safety, tolerability and pharmacokinetic profile of four intravenous doses infused over a 10 minute interval
Study Population	N=28 Healthy subjects Age: 18-45 years (mean 29 years) Gender: All males Weight: 58.2-84 kg (mean 78.48 kg) Race: All White
Treatment Group	Four Dose Groups (50, 100, 150 and 300 mg) 6 on drug and 1 on placebo in each group
Dosage and Administration	Subjects fasted overnight and until 2 hours after dosing. Doses were infused over a 10 minute interval. The volume of injectable was 20 ml, therefore the rate of infusion [120 ml/h] was constant for the doses 50, 100 and 150 mg. The volume of injectable for the 300 mg dose was 30 ml, therefore the rate of infusion for this dose was 180 ml/h. The study drug was supplied in ampoules containing 55 mg of lyophilized material for reconstitution with sterile water. Batch: SP#HFR001 Washout: Wash-Out Phase of at least 14 days between dose treatments
Sampling: Blood	For Lacosamide (ADD 234037): At pre dose and at 10, 20, 30, 40, 50 min, 1, l.5, 2. 3, 4, 5, 6, 8, 10, 12, and 24 h post dose. Groups 2, 3, and 4 (100, 150 and 300 mg doses) had an additional sample taken at 4S h post dose
Urine	none
Feces	none
Analysis	There was no analytical validation report associated with this study report
PK Assessment	Lacosamide in plasma

	Primary PK parameters were: • AUC(0-t), Cmax t1/2, CL, Vd of lacosamide in plasma
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetics of lacosamide in plasma

The mean plasma concentration profile is shown in the following Figure:



Mean pharmacokinetic parameters of all the four doses after IV administration are presented in the following Table:

APPEARS THIS WAY
ON ORIGINAL

Dose	50 mg	100 mg	150 mg	300 mg
Cmax (ng/mL)				
Mean	1428.3	3808.3	5800.0	11796.0
SD	583.2	1273.5	1865.4	2548.7
Median	1205.0	3704.0	6050.0	12500.0
CV%	40.8	33.4	32.2	21.6
Minimum	1070.0	2160.0	3540.0	8670.0
Maximum	2610.0	5460.0	8710.0	14500.0
N	6	6	6	5
Tmax (h)				
Mean	0.473	0.418	0.280	0.170
SD	0.520	0.534	0.201	0.000
Median	0.250	0.170	0.170	0.170
CV%	109.832	127.591	71.962	0.000
Minimum	0.170	0.170	0.170	0.170
Maximum	1.500	1.500	1.500	0.170
N	6	6	6	5
AUC_{0-T} (h·ng/mL)				
Mean	14245.2	39274.9	57685.1	103456.6
SD	1554.5	6961.5	10452.8	11157.9
Median	14227.2	40062.2	56216.9	104006.7
CV%	10.9	17.7	18.1	10.8
Minimum	12446.2	29275.6	45989.7	92180.5
Maximum	16301.3	47546.8	73842.8	116995.9
N	6	6	6	5
$AUC_{0-\infty}$ (h·ng/mL)				
Mean	20259.5	44275.4	62269.1	110983.7
SD	2470.0	6568.2	13253.3	12302.1
Median	19515.1	44959.9	60679.3	113136.1
CV%	12.2	14.8	21.3	11.1
Minimum	17700.9	36160.8	47301.2	97221.7
Maximum	24392.4	53913.2	84006.3	125597.5
N	6	6	6	5
Cl (L/h)				
Mean	2.50	2.30	2.50	2.73
SD	0.28	0.34	0.50	0.31
Median	2.56	2.23	2.49	2.65
CV%	11.38	14.90	20.07	11.21
Minimum	2.05	1.85	1.79	2.39
Maximum	2.82	2.77	3.17	3.09
N	6	6	6	5

Dose	50 mg	100 mg	150 mg	300 mg
Varea (L)				
Mean	48.6	39.4	43.3	48.5
SD	6.8	5.0	5.1	5.4
Median	48.3	39.7	41.4	50.3
CV%	13.9	12.7	11.9	11.1
Minimum	40.5	31.5	39.8	42.4
Maximum	57.5	46.4	53.4	54.8
N	6	6	6	5
Lambdaz (/h)				
Mean	0.052	0.060	0.058	0.056
SD	0.007	0.015	0.011	0.004
Median	0.050	0.056	0.056	0.056
CV%	12.633	25.449	18.716	6.518
Minimum	0.047	0.045	0.044	0.051
Maximum	0.064	0.088	0.075	0.061
N	6	6	6	5
Thalf (h)				
Mean	13.52	12.15	12.34	12.34
SD	1.51	2.62	2.25	0.81
Median	13.88	12.36	12.41	12.32
CV%	11.19	21.60	18.20	6.56
Minimum	10.80	7.90	9.28	11.31
Maximum	14.78	15.54	15.66	13.49
N	6	6	6	5

Mean Cmax increased with increasing dose. The increase was approximately dose proportional.
The mean Tmax decreased with increase in dose.
The AUC also increased in an approximately dose proportional manner.
No dose related trend was observed in the volume of distribution.
The T1/2 was similar across dose groups.

Conclusions:

Lacosamide when administered as IV infusions of 50, 100, 150 and 300 mg over 10 minutes, demonstrated dose dependent pharmacokinetics with an elimination half life of about 13 hours.

DRUG DRUG INTERACTIONS WITH ANTIEPILEPTICS

Study SP601: Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of SPM 927 (harkoseride) on valproic acid (VPA) in 16 healthy male Caucasian volunteers

Objectives:

- The main objective of this trial was to evaluate the effect of SPM 927 on the steady state pharmacokinetics of valproic acid.
- An additional objective was to evaluate the tolerability during the simultaneous dosage of these two anti-epileptic drugs.

The study design is as follows:

Trial Site	[redacted] b(4)
Study Design	This was an open-label, randomized, multiple-dose, 2-way crossover trial in healthy subjects
Study Population	N=16 Healthy subjects randomized Age: 22-44 years (mean 31.3 years) Gender: All males Weight: 58-102 kg (mean 79.9 kg) Race: All White

Treatment Group	<table><tr><th colspan="3">Sequence group I</th><th colspan="3">Sequence group II</th></tr><tr><th>Day</th><th>VPA mg</th><th>SPM 927 mg</th><th>Day</th><th>VPA mg</th><th>SPM 927 mg</th></tr><tr><td>1</td><td>2 x 150</td><td></td><td>1</td><td>2 x 150</td><td></td></tr><tr><td>2</td><td>2 x 150</td><td></td><td>2</td><td>2 x 150</td><td></td></tr><tr><td>3</td><td>2 x 150</td><td></td><td>3</td><td>2 x 150</td><td></td></tr><tr><td>4</td><td>2 x 300</td><td></td><td>4</td><td>2 x 300</td><td></td></tr><tr><td>5</td><td>2 x 300</td><td></td><td>5</td><td>2 x 300</td><td>1 x 100 [1]</td></tr><tr><td>6</td><td>2 x 300</td><td></td><td>6</td><td>2 x 300</td><td>2 x 100</td></tr><tr><td>7</td><td>2 x 300</td><td></td><td>7</td><td>2 x 300</td><td>2 x 200</td></tr><tr><td>8</td><td>2 x 300</td><td></td><td>8</td><td>2 x 300</td><td>2 x 200</td></tr><tr><td>9</td><td>2 x 300</td><td></td><td>9</td><td>2 x 300</td><td>2 x 200</td></tr><tr><td>10</td><td>2 x 300</td><td></td><td>10</td><td>2 x 300</td><td>2 x 200</td></tr><tr><td>11</td><td>2 x 300</td><td>1 x 100 [1]</td><td>11</td><td>2 x 300</td><td>1 x 200 [2]</td></tr><tr><td>12</td><td>2 x 300</td><td>2 x 100</td><td>12</td><td>2 x 300</td><td></td></tr><tr><td>13</td><td>2 x 300</td><td>2 x 200</td><td>13</td><td>2 x 300</td><td></td></tr><tr><td>14</td><td>2 x 300</td><td>2 x 200</td><td>14</td><td>2 x 300</td><td></td></tr><tr><td>15</td><td>2 x 300</td><td>2 x 200</td><td>15</td><td>2 x 300</td><td></td></tr><tr><td>16</td><td>2 x 300</td><td>2 x 200</td><td>16</td><td>2 x 300</td><td></td></tr><tr><td>17</td><td>1 x 300</td><td>1 x 200 [2]</td><td>17</td><td>1 x 300</td><td></td></tr><tr><td>18</td><td></td><td></td><td>18</td><td></td><td></td></tr><tr><td>19</td><td></td><td></td><td>19</td><td></td><td></td></tr><tr><td>20</td><td></td><td></td><td>20</td><td></td><td></td></tr></table> 1 Administration of SPM 927 in the evening 2 Administration of SPM 927 in the morning Sequence group II, period 1: Monotherapy with VPA, period 2: Co-administration of SPM 927, added to period 1: Second period monotherapy with VPA.
Dosage and Administration	Except where otherwise indicated, the doses were split equally between morning (about 8:00) and evening (12 h later, about 20:00). SPM 927 capsules Batch No: WE 11559 Valproic acid Batch No: WE 11587 Diet: Caffeine containing food and drink (coffee, tea, cola, cocoa, chocolate), grapefruit, quinine containing products (Schweppes Tonic Water) should not be taken from 24 h before the preliminary examination and from 24 h before check-in up to the end of the experimental part of the study. No smoking was allowed. Standardized meals were provided. No breakfast was served on the Days of pharmacokinetic profiling (Days 11, 17)
Sampling: Blood	For VPA: Trough levels of valproic acid are measured in samples taken before dosage on Days 1 (blank), 3, 5, 7, 8, 10, 11, 13, 14, 16 and 17. On days 11 and 17 additional samples will be taken. Day11: Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 12 hours postdose

	Day17: Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours postdose
Urine	none
Feces	none
Analysis	Method: LC.MS/MS method in plasma Lower Limits of Quantitation: Plasma VPA 0.1 µg/mL Plasma: Linear Range: 0.10-50 µg/ml in plasma Quality control concentrations 0.2, 5, 40 µg/ml Inter-day precision: < 4.11 %CV Inter-day accuracy: -1.69 to 1.13 % bias Recovery: 90-100% Stability: 3 freeze-thaw cycles, up to 4 hours at room temp, injection vial at 4°C for at least 12 hours
PK Assessment	Parameters for Valproic Acid: AUC(0-tz), AUC(0-12), t1/2, tmax, Cmax, tmax, AUMC0-12, Cltot/f, Vz/f, MRT
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Effect of multiple doses of LCM on Steady state pharmacokinetics of valproic acid in plasma:

Due to expected CNS adverse events of both drugs (VPA and SPM 927 or LCM) a relatively low target dose of VPA (600 mg/day) was selected. For tolerability reasons dosing was started with a valproic acid dose of 300 mg/day. The half-life of valproic acid is 12-16 hours, hence multiple doses of VPA up to 11 days is adequate for it to reach steady state levels.

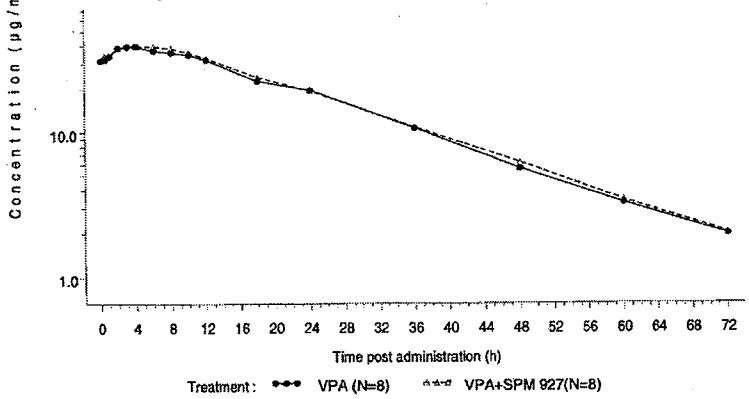
The following table summarizes the primary pharmacokinetic parameters of valproic acid after administration of 300 mg slow-release VPA bid given alone or during co-administration of 200 mg SPM 927 given twice daily on Day 11 or 17. There was no evidence of sequence effects.

Pharmacokinetic parameters of valproic acid in plasma:

		N	$AUC_{0\rightarrow12,ss}$ (µg·h/ml) Mean	SD	$C_{max,ss}$ (µg/ml) Mean	SD	$t_{max,ss}$ (h) Median	Range	$t_{1/2}$ Following last administration (h) Median	Range
Sequence group I	VPA	8	410.3	94.1	38.3	8.0	3.1	(2.0-4.0)		
	VPA+SPM 927	8	429.1	76.9	40.1	7.2	6.0	(2.0-10.0)	13.5	(11.8-20.0)
Sequence group II	VPA	8	456.4	71.1	44.6	6.8	4.0	(2.0-6.0)	14.4	(10.6-22.0)
	VPA+SPM 927	8	468.7	100.6	44.1	9.8	3.5	(2.0-10.0)		
Total	VPA	16	433.4	84.0	41.4	7.9	3.0	(2.0-6.0)		
	VPA+SPM 927	16	448.9	88.9	42.1	8.6	5.0	(2.0-10.0)		

The following figure shows that mean plasma concentration profile for VPS with or without coadministration of LCM.

Figure R1 Mean plasma concentrations of valproic acid following multiple doses of VPA with and without co-administration of SPM 927



The results of the statistical analysis are shown in the following Table:

Statistical Analysis (ANOVA)

Parameter	Comparison	Point estimate	90 % CI
$AUC_{0\text{-}12h,\ ss}$	VPA with / without SPM 927	1.04	(0.99, 1.09)
$C_{max,ss}$	VPA with / without SPM 927	1.01	(0.97, 1.07)

VPA population pooled from VPA (alone) before and after SPM 927 co-administration

These results show that there was no effect of multiple dosing of lacosamide on the steady state pharmacokinetics of valproic acid. The 90% confidence interval were within the acceptable limits of 85-125%

Safety:

Sequence II, in which LCM was administered after 4 days of dosing on VPA had higher adverse events compared to Sequence I in which VPA was administered for a longer duration of 11 days. The reason for this is not clear, because in both sequences VPA would be at steady state. Most common AE reported was headache, hot flushes, dizziness.

The following Table provides the overview of AEs in this study according to the sponsor. The medical officer will further evaluate the AEs.

Summary of adverse events by treatment conditions

	Sequence Group I	Sequence Group II	Total Number
Number of subjects	8	8	16
completers	8	8	16
drop-outs	0	0	0
Number of subjects with AEs	5	7	12
subjects with AEs after VPA	5	4	9
subjects without AEs after VPA	3	4	7
subjects with AEs after VPA + SP 927	4	7	11
subjects without AEs after VPA + SP 927	4	1	5
AE episodes	29	66	95
AE episodes after VPA	18	18	36
AE episodes after VPA + SP 927	11	48	59
AEs	24	44	68
AE after VPA *	16	15	31
AE after SP 927 + VPA *	8	29	37

Conclusion:

There was no effect of SPM 927 on the steady state pharmacokinetics of valproic acid (VPA) observed in this trial. No dosage adjustment is necessary.

Study SP602: Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of valproic acid (VPA) on SPM 927 (harkoseride) in 16 healthy male Caucasian volunteers

Objectives:

- The main objective of this trial was to evaluate the effect of valproic acid on the steady state pharmacokinetics of SPM 927.
- An additional objective was to evaluate the tolerability during the simultaneous dosage of these two anti-epileptic drugs.

The study design is as follows:

b(4)

Trial Site	[redacted]
Study Design	This was an open-label, randomized, multiple-dose, 2-way crossover trial in healthy subjects
Study Population	N=16 Healthy subjects randomized Age: 21-44 years (mean 29.9 years) Gender: All males Weight: 64-95.5 kg (mean 79.1 kg) Race: All White

Treatment Group	

Sequence group I			Sequence group II		
Day	SPM 927 mg	VPA mg	Day	SPM 927 mg	VPA mg
1	2 x 200		1	2 x 200	
2	2 x 200	2 x 150	2	2 x 200	
3	2 x 200	2 x 150	3	2 x 200	
4	2 x 200	2 x 150	4	2 x 200	
5	2 x 200	2 x 300	5	2 x 200	
6	2 x 200	2 x 300	6	2 x 200	
7	2 x 200	2 x 300	7	2 x 200	
8	2 x 200	2 x 300	8	2 x 200	
9	2 x 200	2 x 300	9	2 x 200	
10	2 x 200	2 x 300	10	2 x 200	2 x 150
11	2 x 200	2 x 300	11	2 x 200	2 x 150
12	2 x 200	2 x 300	12	2 x 200	2 x 150
13	2 x 200	2 x 300	13	2 x 200	2 x 300
14	2 x 200	1 x 300	14	2 x 200	2 x 300
15	2 x 200		15	2 x 200	2 x 300
16	2 x 200		16	2 x 200	2 x 300
17	2 x 200		17	2 x 200	2 x 300
18	2 x 200		18	2 x 200	2 x 300
19	2 x 200		19	2 x 200	2 x 300
20	2 x 200		20	2 x 200	2 x 300
21	2 x 200		21	2 x 200	2 x 300
22	1 x 200		22	1 x 200	1 x 300

Dosage and Administration	Doses were split equally between morning (about 8:00) and evening (12 h later, about 20:00). On Day 22, doses were given only in the morning. SPM 927 capsules Batch No: WE 11559 Valproic acid Batch No: WE 11587 Diet: Caffeine containing food and drink (coffee, tea, cola, cocoa, chocolate), grapefruit, quinine containing products (Schweppes Tonic Water) should not be taken from 24 h before the preliminary examination and from 24 h before check-in up to the end of the experimental part of the study. No smoking was allowed. Standardized meals were provided. No breakfast was served on the Days of pharmacokinetic profiling
Sampling: Blood	Group 1: Trough levels of valproic acid are measured in samples taken before dosage (ca. 08:00) on Days 1 (blank), 3, 5, 7, 9, 11, and 13. Trough levels of harkoseride are measured in samples taken predose on Days 1(blank), 3, 5, 7, 9, 11, 13, 14, 21 and 22. Additional samples are taken 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h postdose on Days 14 and 22 and 18, 24, 36, 48, 60 and 72 h after the final dose on Day 22. Group 2:

	Trough levels of valproic acid are measured in samples taken before dosage (ca. 08:00) on Days 1 (blank), 11, 13, 15, 17, 19 and 21. Trough levels of harkoseride are measured in samples taken predose on Days 1 (blank), 8, 9, 11, 13, 15, 17, 19, 21 and 22. Additional samples are taken 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h postdose on l3ays 9 and 22 and 18, 24, 36, 48, 60 and 72 h after the final dose on Day 22.
Urine	none
Feces	none
Analysis	Method: LC.MS/MS method in plasma Lower Limits of Quantitation: Plasma SPM927 0.1 µg/mL SPM927 in Plasma: Linear Range: 0.10-20 µg/ml in plasma Quality control concentrations 0.3, 1.5, 15 µg/ml Inter-day precision: < 7.8 %CV Inter-day accuracy: -5.1 to 6.8 % bias
PK Assessment	Parameters for SPM 927: AUC(0-tz), AUC(0-12), t1/2, tmax, Cmax, tmax, AUMC0-12, Cltot/f, Vz/f, MRT
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	None

Pharmacokinetic Results:

Effect of multiple doses of VPA on Steady state pharmacokinetics of Lacosamide in plasma:

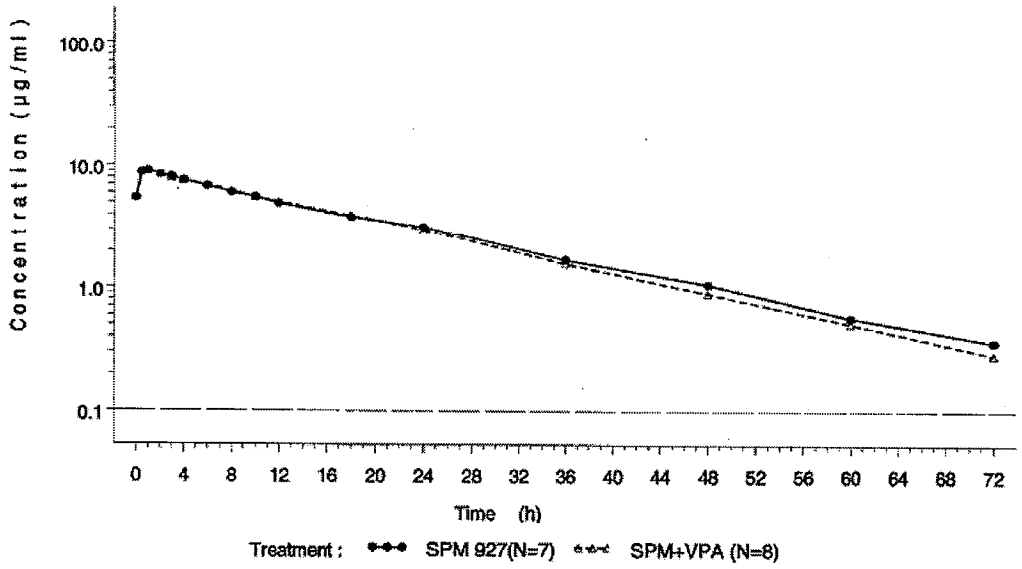
The pharmacokinetic characteristics of SPM 927 were similar when given alone or together with VPA. This was true for the mean values of AUCss, Cmax,ss, tmax and t1/2 (see following Table).

There was no evidence of any sequence or period effects, i.e. there was no difference between pharmacokinetic results obtained when SPM 927 was given alone first or given in combination with VPA first. Plasma concentration-time curves for SPM 927 given alone or in combination with VPA were virtually superimposable (see Figure below).

Pharmacokinetic parameters of SPM927 in plasma:

		N	$AUC_{0\rightarrow12,ss}$ (µg·h/ml)		$C_{max,ss}$ (µg/ml)		t_{max} (h)		$t_{1/2}$ Following last administration (h)	
			Mean	SD	Mean	SD	Median	Range	Median	Range
Sequence group I	SPM 927	8	85.7	13.9	9.9	1.1	1.0	(0.5-1.0)	15.6[2]	(10.7-19.1)
	SPM 927 + VPA	8	83.8	12.0	9.9	0.9	0.5	(0.5-1.0)		
Sequence group II	SPM 927	8	80.1	14.2	9.2	1.4	0.5	(0.5-1.0)		
	SPM 927 + VPA	8	82.1	16.1	9.6	1.4	1.0	(0.5-3.0)	13.2	(10.7-18.7)
Total	SPM 927	16	82.7	13.9	9.5	1.3	0.5	(0.5-1.0)		
	SPM 927 + VPA	16	82.9	13.8	9.7	1.2	0.8	(0.5-3.0)		

Mean plasma concentration of SPM 927 following multiple doses of SPM 927 with or without co-administration of valproic acid



The results of the statistical analyses are summarized in the following Table:

Summary of Statistical Analyses

Parameter	Comparison	Point estimate	90% CI
$AUC_{(0\text{-}12h),\ ss}$	SPM 927 with / without VPA	1.00	(0.98, 1.03)
$C_{max,\ ss}$	SPM 927 with / without VPA	1.01	(0.96, 1.07)

SPM 927 population pooled from SPM 927 (alone) before and after VPA co-administration

These 90% estimates fall well into the conventional bioequivalence range (80-125%) for Cmax and AUC, and there was no difference in tmax and t1/2. Therefore it can be concluded that there was no effect of VPA on the steady-state pharmacokinetics of SPM 927.

Trough values of VPA on Days 9, 11, and 13 (sequence group I) or on Days 17, 19, and 21 (group II) were almost identical, indicating that steady-state was reached. Figure R2 summarizes the individual through levels from Day 3 to 13 (group I) and Day 11 to 21 (group I) after oral administration of VPA. The inspection of the curves revealed an unexpected high concentration in subject 8013 and a low concentration in subject 8012 on day 19. Although the reason for this could not be verified, the sponsor believes that it could be possible that samples from the two subjects were exchanged before analysis.

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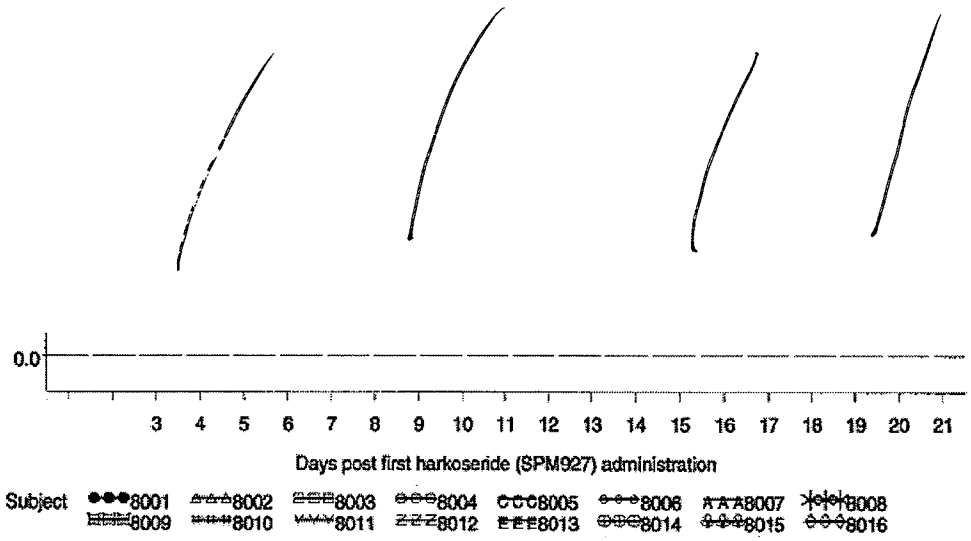
VPA individual trough levels from Day 3 to Day 21



Safety:

The adverse events for the groups I and II is given below:

Summary of adverse events by treatment conditions SPM 927 vs. SPM 927 + VPA

	Sequence Group I	Sequence Group II	Total Number
Number of subjects completers drop-outs	8 7 1	8 8 0	16 15 1
Number of subjects with AEs subjects with AEs after SPM 927 subjects without AEs after SPM 927 subjects with AEs after SPM 927 + VPA subjects without AEs after SPM 927 + VPA	8 5 3 7 1	8 7 1 8 0	16 12 4 15 1
AE episodes AE episodes after SPM 927 AE episodes after SPM 927 + VPA	46 18 28	55 32 23	101 45 56
AEs AE after SPM 927 AE after SPM 927 + VPA	40 17 23	45 26 19	85 43 42

Under treatment with SPM 927 alone, and in combination with VPA group I showed 17/23 and group II 26/1 9 AEs. In group II, AEs were fewer when SPM927 and VPA were coadministered.

Conclusions:

There was no effect of valproic acid (VPA) on the steady-state pharmacokinetics of SPM 927.

Study SP618: Open-label multiple dose study to evaluate the effect of SPM 927 (harkoseride) on the pharmacokinetics carbamazepine (CBZ) in 20 healthy male Caucasian volunteers

Objectives:

- The main objective of this study was to evaluate the effect of SPM 927 on the steady state pharmacokinetics of carbamazepine.
- An additional objective was to document adverse events during the simultaneous dosage of the two anti-epileptic drugs.

The study design is as follows:

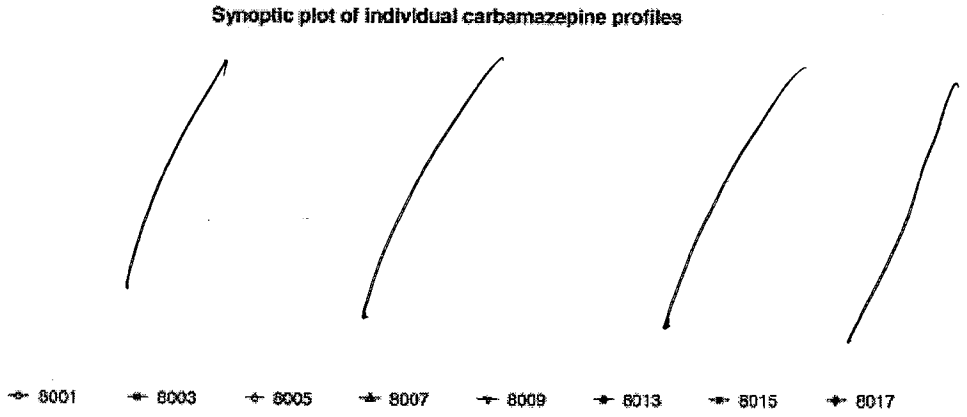
Trial Site	b(4)
Study Design	This was an open-label, randomized, multiple-dose, 2-way crossover trial in healthy subjects
Study Population	N=20 Healthy subjects randomized. There were two drop-outs during this study; in one case due to an adverse event (rash erythematous, not related to the intake of SPM 927); in the other one due to personal reasons. Both subjects were not substituted. Age: 23-43 years (mean 33.9 years) Gender: All males Weight: 71.2-98.8 kg (mean 79.49 kg) Race: All White
Treatment Group	All subjects were treated with carbamazepine from Day 1 to Day 22. Group 1 received SPM 927 for one week starting on Day 7. Group 2 received SPM 927 for one week starting on Day 15.
Dosage and Administration	For reasons of tolerability, the dose of SPM 927 raised from 100 mg twice daily over 2 days to 200 mg twice daily. The dose of carbamazepine raised from 100 mg twice daily over 3 days to 200 mg twice daily until Day 22. At each administration, carbamazepine alone or in combination with SPM 927 was swallowed with 200 ml tap water of room temperature. The precise time of each administration was recorded. SPM 927 capsules, 100mg, Batch No: WE 11559 Carbamazepine sustained release tablet —, 200 mg: Batch No: WE 11598 b(4) Diet: Caffeine containing food and drink (coffee, tea, cola, cocoa, chocolate), grapefruit, quinine containing products (Schweppes Tonic Water) should not be taken from 24 h before the preliminary examination. No smoking was allowed. Standardized meals were provided (Days 14 and 22). During their hospitalization, the subjects will fast overnight. One hour prior to each morning administration the subjects will start to eat breakfast.

Sampling: Blood	For CBZ Day -1, 3, 5, 7, 9, 11, 13 (am, pm), , 15, 17, 19, 21(am, pm) Day14 : Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 12 hours postdose Day 22: Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours postdose
Urine	none
Feces	none
Analysis	Method: LC.MS/MS method in plasma Lower Limits of Quantitation: Plasma CBZ 0.05 µg/ml CBZ-epoxide 0.025 µg/ml Plasma: Linear Range: 0.05-5 µg/ml in plasma for CBZ, 0.025-5 µg/ml Quality control concentrations 0.08, 0.20, 0.40, 2.0 and 4.0 µg/ml for CBZ, 0.04, 0.4, 0.8, 2.0 µg/ml for CBZ epoxide Inter-day precision: < 2.95 %CV for CBZ and <3.4% for CBZ-epoxide Inter-day accuracy: -4.48 to 1.62% bias Recovery: 92.6% for CBZ Stability: Plasma samples were stable at room temperature, under refrigerator conditions (2°C - 8°C) and freezer conditions (-20°C ± 5°C, for at least 72 h. Spiked samples in freezer for at least 55 days, 6 freeze-thaw cycles
PK Assessment	Parameters for CBZ: AUCss(0-tz), t1/2, tmax,ss, Cmax,ss, Cmin,ss, Ctrough
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	saccadiac eye movement: Days 6, 9, 13, 17, 21 and 24

Pharmacokinetic Results:

Effect of multiple doses of LCM on Steady state pharmacokinetics of CBZ in plasma:

The full PK profile for CBZ from Day -1 of the study is shown in the following Figures for Group I (SPM 927 dosing days 7-14) and Group 2 (SPM 927 dosing days 15-22):



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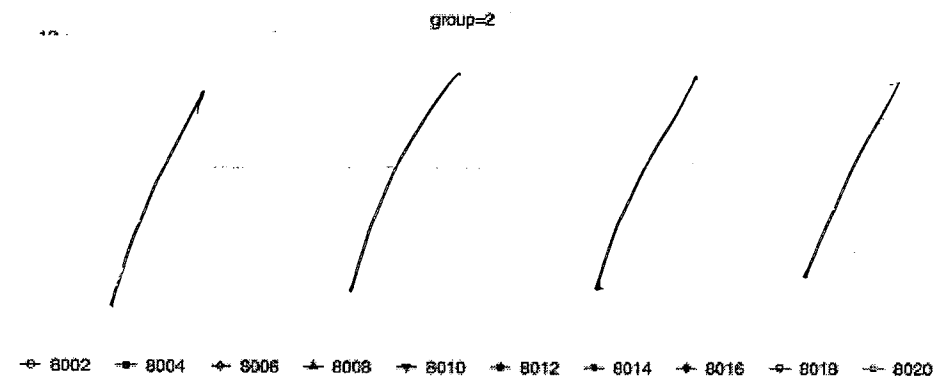

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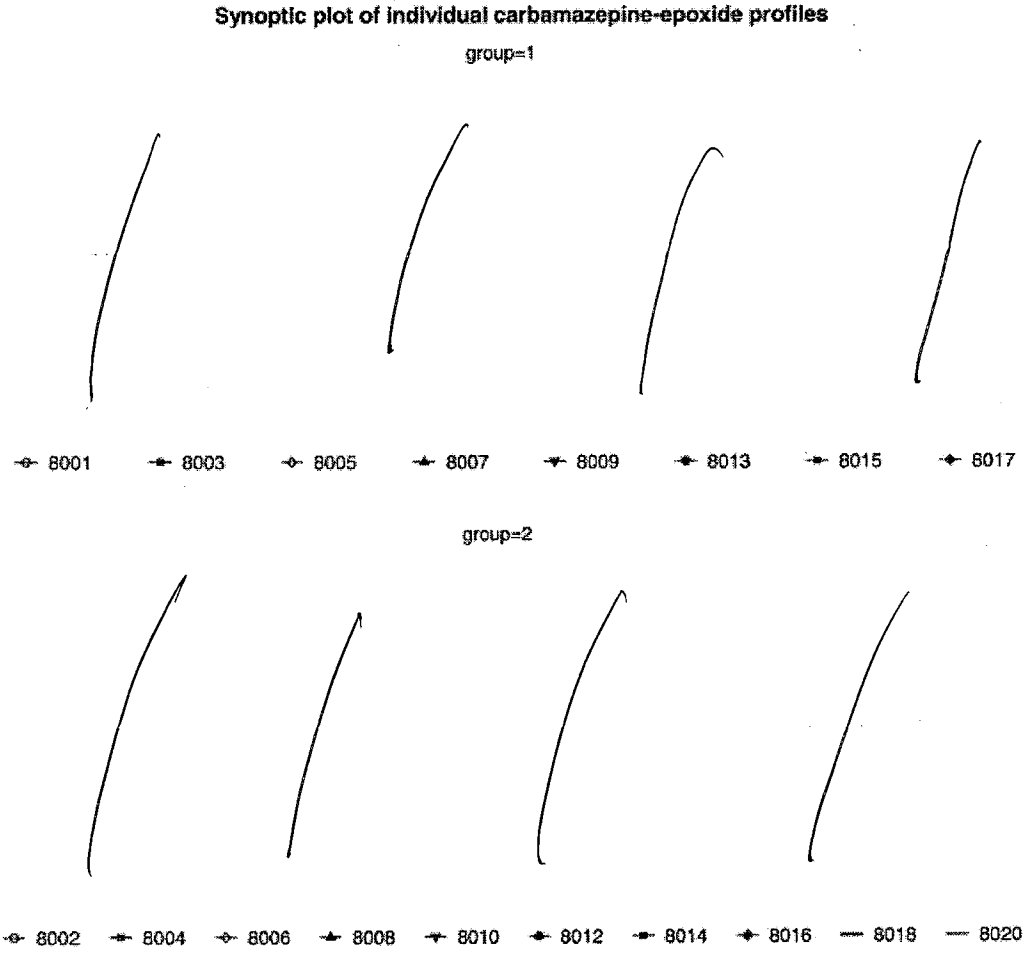
Trough carbamazepine concentrations increased for both groups reaching plateau values on Day 6-8 after start of carbamazepine administration. There was a trend for the carbamazepine concentrations to slightly decrease thereafter for both groups. This finding was independent of the co-administration of SPM 927, as subjects of Group 1 started with the co-administration on Day 7 and the subjects of Group 2 on Day 15.

For Group 1 the systemic exposure to carbam8zepine decreased by 6.8% from Day 14 to Day 22.

For Group 2 the systemic exposure to carbamazepine decreased by 12.1% from Day 14 to Day 22.

The full PK profile for CBZ-epoxide from Day -1 of the study is shown in the following Figures for Group I (SPM 927 dosing days 7-14) and Group 2 (SPM 927 dosing days 15-22):



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Trough carbamazepine-epoxide concentrations increased for both groups reaching plateau values on Day 8 after start of carbamazepine administration.

The pharmacokinetic parameters carbamazepine and carbamazepine-epoxide are shown in the following Table:

PK day	PK parameter / unit	<<	Group 1 N	arithm. Mean	SD	Geo. Mean	>> <<	Group 2 N	arithm. Mean	SD	Geo. Mean >>
carbamazepine											
14	AUC_{ss} (µg*h/ml)		8	56.58	9.11	55.93		10	71.95	21.87	69.31
	$C_{max,ss}$ (µg/ml)		8	5.10	0.80	5.04		10	6.41	1.88	6.19
	$t_{max,ss}$ (h)		8	3.00	0.93	2.87		10	2.90	1.84	2.17
22	AUC_{ss} (µg*h/mL)		8	52.67	8.17	52.10		10	62.35	15.08	60.94
	CL (l/min)		8	0.0647	0.0105	0.0640		10	0.0558	0.0112	0.0547
	$C_{max,ss}$ (µg/ml)		8	4.67	0.71	4.62		10	5.76	1.38	5.63
	$C_{min,ss}$ (µg/ml)		8	4.03	0.66	3.98		10	4.66	1.27	4.52
	C_{trough} (µg/ml)		8	0.44	0.09	0.44		10	0.52	0.10	0.51
	λz (1/h)		8	0.0276	0.0044	0.0273		10	0.0245	0.0048	0.0240
	$t_{1/2}$ (h)		8	25.69	3.94	25.42		10	29.40	6.29	28.83
	$t_{max,ss}$ (h)		8	4.25	1.17	4.12		10	3.80	0.42	3.78
	V_z (l)		8	141.36	13.30	140.81		10	137.33	16.59	136.48
carbamazepine-epoxide											
14	AUC_{ss} (µg*h/ml)		8	5.57	1.29	5.44		10	6.16	1.08	6.07
	$C_{max,ss}$ (µg/ml)		8	0.51	0.12	0.49		10	0.57	0.10	0.56
	$t_{max,ss}$ (h)		8	3.31	3.35			10	3.05	2.73	
22	AUC_{ss} (µg*h/mL)		8	5.09	0.94	5.01		10	5.90	1.00	5.82
	CL (l/min)		8	0.6744	0.1214	0.6647		10	0.5795	0.0944	0.5724
	$C_{max,ss}$ (µg/ml)		8	0.46	0.08	0.46		10	0.54	0.09	0.53
	$C_{min,ss}$ (µg/ml)		8	0.39	0.08	0.38		10	0.44	0.08	0.44
	C_{trough} (µg/ml)		8	0.44	0.09	0.44		10	0.52	0.10	0.51
	λz (1/h)		8	0.0333	0.0051	0.0329		10	0.0320	0.0057	0.0315
	$t_{1/2}$ (h)		8	21.30	3.47	21.06		10	22.33	4.05	22.00
	$t_{max,ss}$ (h)		8	3.44	3.27			10	3.40	2.99	
	V_z (l)		8	1235.26	244.57	1211.47		10	1107.78	195.07	1090.46

The statistical assessment of the effect of SPM927 of the pharmacokinetics of carbamazepine in Group I is given in the following Table. This comparison is of Day 14 (SPM 927+CBZ) and Day 22 (CBZ alone).

The following Table shows that SPM927 was at steady state after 3 days of dosing in the two dose groups based on the trough concentrations:

group	time (h)	N	Mean	SD
1	240	8	5.00	0.72
	288	8	4.96	0.76
	300	8	4.43	0.66
	312	8	4.91	0.86
	324	8	4.56	0.85
2	432	10	5.09	1.13
	480	10	5.24	1.09
	492	10	4.63	1.38
	504	10	5.26	1.33
	516	10	4.47	1.05

Parameter	Comparison	Point estimate	90% CI
CBZ			
AUC_{ss}	CBZ with / without SPM 927	1.07	1.04-1.11
$C_{max,ss}$	CBZ with / without SPM 927	1.09	1.04-1.14
CBZ-epoxide			
AUC_{ss}	CBZ with / without SPM 927	1.09	0.84-1.01
$C_{max,ss}$	CBZ with / without SPM 927	0.92	0.84-1.11

The statistical assessment of the effect of SPM927 of the pharmacokinetics of carbamazepine in Group I is given in the following Table. This comparison is of Day 14 (CBZ alone) and Day 22 (SPM 927+CBZ).

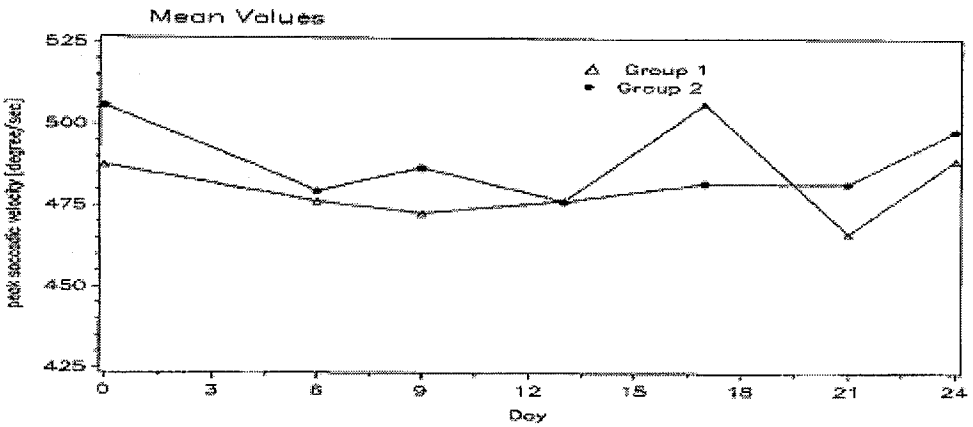
Parameter	Comparison	Point estimate	90% CI
CBZ			
AUC_{ss}	CBZ with / without SPM 927	0.88	0.84-0.92
$C_{max,ss}$	CBZ with / without SPM 927	0.91	0.87-0.98
CBZ-epoxide			
AUC_{ss}	CBZ with / without SPM 927	0.97	0.89-1.04
$C_{max,ss}$	CBZ with / without SPM 927	0.95	0.87-1.05

In both Group 1 and 2, the 90% confidence intervals were within the acceptable bioequivalence limits, suggesting that there was no effect of SPM 927 on the pharmacokinetics of carbamazepine.

Pharmacodynamics:

The peak saccadic velocity (PSV), that is the maximum velocity of eye movement in terms of degree per second, was selected to be the primary parameter for the measurement of a possible influence of SPM 927 and/or carbamazepine on the eye motility.

The mean peak saccadiac velocity [degree/sec] is shown in the following figure:



The mean and SD of the Saccadic Eye Movements is shown in the following Table:

Group	Day	N	Mean	SD
1	0	8	487.54	55.50
	6	8	476.51	60.20
	9	8	472.76	61.52
	13	8	476.83	65.85
	17	7*	506.47	39.00
	21	8	466.69	64.23
	24	8	489.11	57.51
2	0	10	505.68	41.92
	6	10	479.63	42.18
	9	10	486.72	43.56
	13	10	476.44	39.46
	17	10	482.20	48.51
	21	10	482.06	51.46
	24	10	498.12	56.06

The following Table shows the mean changes from baseline PSV values along with the 95% confidence intervals:

	change from baseline	p	lower 95% conf.	upper -int.
			GROUP=1	
Day 6 - Day 0	-11.0	0.7050	-69.2	47.2
Day 9 - Day 0	-14.8	0.6163	-73.7	44.1
Day 13 - Day 0	-10.7	0.7265	-71.9	50.5
Day 17 - Day 0	18.9	0.4442	-30.4	68.3
Day 21 - Day 0	-20.8	0.4906	-81.2	39.6
Day 24 - Day 0	1.6	0.9558	-55.2	58.4
			GROUP=2	
Day 6 - Day 0	-26.0	0.1709	-63.6	11.5
Day 9 - Day 0	-19.0	0.3251	-57.2	19.2
Day 13 - Day 0	-29.2	0.1132	-65.6	7.1
Day 17 - Day 0	-23.5	0.2512	-64.0	17.0
Day 21 - Day 0	-23.6	0.2647	-65.6	18.3
Day 24 - Day 0	-7.6	0.7338	-51.8	36.7

None of these changes in the PSV was significant based on the p values.
Mean peak saccadic velocity varied between 465 and 505 degrees per second. There was no trend with respect to the co-administration of SPM 927.

Safety:

Adverse event profile was similar for the two groups and did not increase with concomitant administration of SPM927 and carbamazepine.

Conclusions:

- There is no influence of SPM 927 on the pharmacokinetics of carbamazepine and its epoxide metabolite.
- SPM 927 had no influence on the peak saccadic eye velocity measured under multiple doses of carbamazepine.

Study SP603: Open-label multiple dose study to evaluate the effect of carbamazepine (CBZ) on the pharmacokinetics SPM 927 (harkoseride)in 20 healthy male Caucasian volunteers

Objectives:

- The main objective of this study was to evaluate the effect of carbamazepine on the steady state pharmacokinetics of SPM 927.
- An additional objective was to document adverse events during the simultaneous dosage of the two anti-epileptic drugs.

The study design is as follows: b(4)

Trial Site	[redacted]
Study Design	This was an open-label, randomized, multiple-dose, 2-way crossover trial in healthy subjects
Study Population	N=20 Healthy subjects selected, 19 randomized Age: 18-42 years Gender: All males Weight: 72-98 kg Race: All White
Treatment Group	All subjects were treated with SPM927 from Day 1 to Day 17. Group 1 received CBZ for 1 week from Day 2-9. Group 2 received CBZ for 1 week from Day 10-17. Carbamazepine showed a long half-life of 36 h (18-65 h), which is reduced by 50% during the enzyme induction observed after long-term therapy with this drug. Steady state conditions are achieved after 2 to 8 days of repeated administration.
Dosage and Administration	The dose of SPM 927 was 200 mg twice daily. The dose of carbamazepine was raised from 100 mg twice daily over 3 days to 200 mg twice daily until Day 17. At each administration, carbamazepine alone or in combination with SPM 927 was swallowed with 200 ml tap water of room temperature. The precise time of each administration was recorded. SPM 927 capsules, 100mg, Batch No: WE 11559 Carbamazepine sustained release tablet [redacted] 200 mg: Batch No: WE 11598 Diet: Caffeine containing food and drink (coffee, tea, cola, cocoa, chocolate), grapefruit, quinine containing products (Schweppes Tonic Water) should not be taken from 24 h before the preliminary examination. No smoking was allowed. Standardized meals were provided (Days 9 and 17). During their hospitalization, the subjects will

b(4)

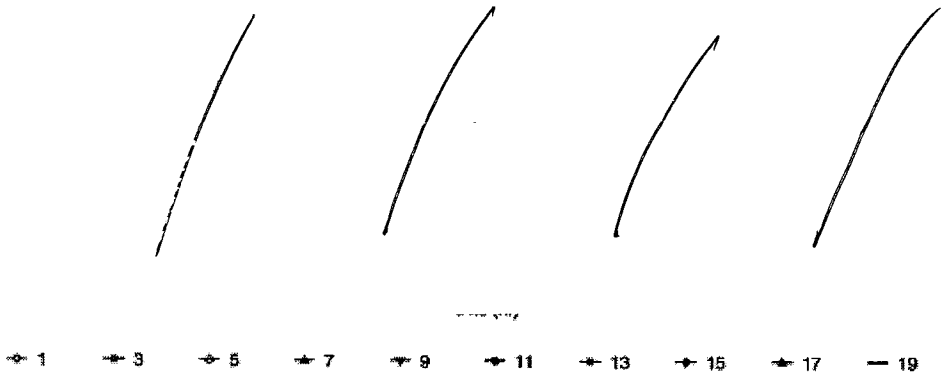
	fast overnight. One hour prior to each morning administration the subjects will start to eat breakfast.
Sampling: Blood	For SPM927: Day -1, 2, 4, 6, 8, 9, 10 (am, pm), 12, 14, 16 (am, pm) Day 9 : Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 10, 12 hours postdose Day 16: Predose (0) and at 0.5, 1.0, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours postdose
Urine	none
Feces	none
Analysis	Method: LC.MS/MS method in plasma Lower Limits of Quantitation: Plasma SPM 927 0.1 µg/mL Plasma: Linear Range: 0.10-20 µg/ml in plasma Quality control concentrations 0.3, 1.5, 15 µg/ml Inter-day precision: < 11.5 %CV Inter-day accuracy: -6.8 to -2.9 % bias
PK Assessment	Parameters for SPM927: AUCss(0-tz), t1/2, tmax,ss, Cmax,ss, Cmin,ss, Ctrough, AUMC, Cltot/f, Vz/f
Safety Assessment	Laboratory tests, adverse events, ECGs
PD Assessment	saccadiac eye movement: Days -1, 4, 8, 12, 16

Pharmacokinetic Results:

Effect of multiple doses of CBZ on Steady state pharmacokinetics of LCM in plasma:

The plasma concentration profiles for the entire study duration is shown in the following figures for Group 1 and 2:

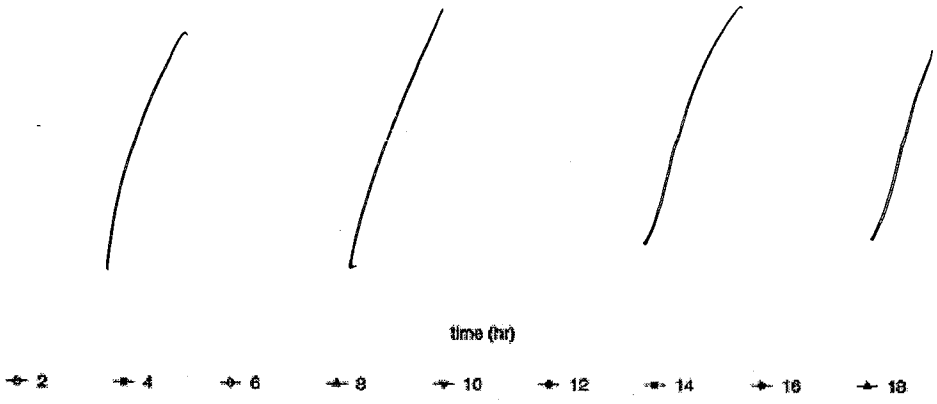
Synoptic plot for individual SPM 927 plasma concentration profile for group 1



b(4)

The trough concentrations observed in Group 1 were higher on Day 9 (5.58 pg/mL) at the end of the carbamazepine co-administration period as compared to Day 17 (4.69 pg/mL) after the wash-out period.

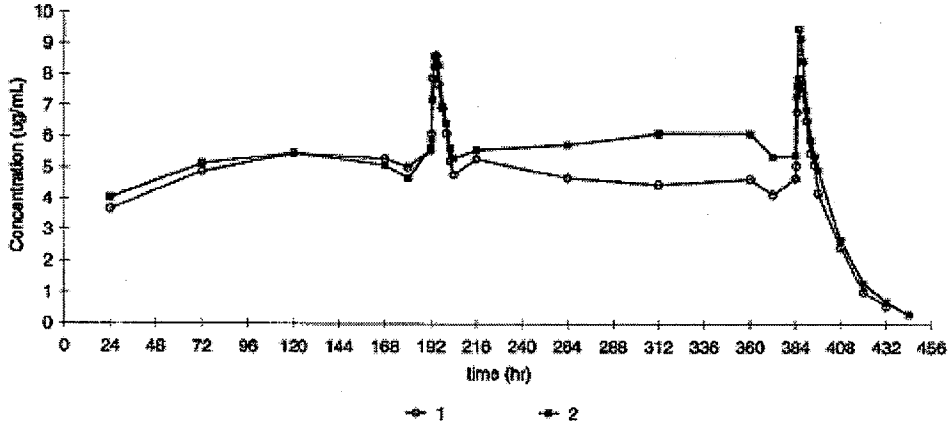
Synoptic plot for individual SPM 927 plasma concentration profile for group 2



b(4)

In Group 2, the trough concentration after co-administration of carbamazepine was slightly lower than after SPM 927 alone. Visual inspection of the synoptic plots of SPM 927 plasma profiles supported by linear regression analysis confirmed steady state conditions at the days 9 and 17 of full pharmacokinetic profiles. The geometric mean profiles of the two groups together showing the differences in trough concentrations are shown in the following Figure:

Figure: Geometric Mean SPM 927 Concentration Profiles for Groups 1 and 2



On Day 9, after group 1 received SPM 927 and carbamazepine while group 2 got only SPM 927, the pharmacokinetic parameters were similar. On day 17 after a one week carbamazepine wash-out phase for group 1 and after group 2 got carbamazepine for one week, the PK profiles for SPM 927 were slightly different. Cmax and AUC were changed, whereas the

terminal mean half- lives estimated for both groups remained identical (12.8 hours). The profile of SPM 927 trough concentrations shows increasing concentrations for group 2 and decreasing concentrations for group 1.

The mean PK parameters are summarized in the following Table:

PK day	PK parameter	<< Group 1 >> N	arithm. Mean	SD	Geometric Mean	<< Group 2 >> N	arithm. Mean	SD	Geometric Mean
9	AUC_{ss} (µg*h/mL)	10	82.16	17.95	80.42	9	83.55	7.62	83.25
	C_{max} (µg/mL)	10	9.35	2.15	9.13	9	9.78	1.30	9.71
	T_{max} (h)	10	2.35	1.16	1.99	9	2.28	1.09	1.96
	C_{trough} (µg/mL)	10	5.72	1.38	5.58		5.70	0.83	5.64
17	AUC_{ss} (µg*h/mL)	10	76.30	16.82	74.57	9	84.53	8.62	84.16
	CL_{tot}/f (L/min)	10	0.05	0.01	0.04	9	0.04	0.00	0.04
	C_{max} (µg/mL)	10	8.46	1.59	8.33	9	10.56	1.73	10.44
	$C_{min,ss}$ (µg/mL)	10	4.29	1.18	4.14	9	4.83	0.71	4.78
	C_{trough} (µg/mL)	10	4.84	1.26	4.69	9	5.46	0.74	5.42
	λ_z (1/h)	10	0.06	0.01	0.05	9	0.05	0.01	0.05
	$t_{1/2}$ (h)	10	12.81	2.04	12.67	9	12.75	1.36	12.68
	T_{max} (h)	10	2.60	0.97	2.42	9	1.83	0.71	1.66
	V_z/f (L)	10	49.57	7.55	49.05	9	43.83	5.94	43.48

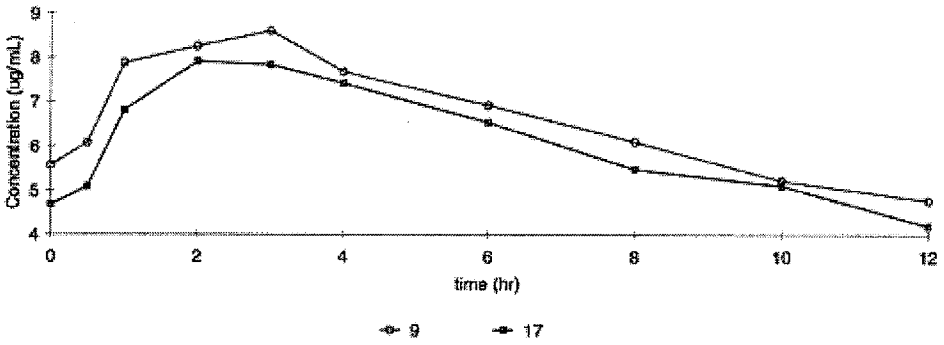
The statistical comparison of Day 9 versus Day 17 within each group is given in the following Table. This Table also shows the comparison between the Groups 1 and 2 on the same sampling day (Day 9, Day 17).

Statistical Assessment on the Effect of Carbamazepine on SPM 927 Pharmacokinetics

Group	Parameter	Day	Geo Mean	Ratio (Day 9/17)	90% CI (Day 9/17)	Ratio (Group1/2)	90% CI (Group1/2)
1	AUCss	9 (with CBZ)	80.42			0.966	0.844-1.106
		17 (w/o CBZ)	74.57	1.079	1.002-1.161	0.886	0.767-1.023
	Cmax	9 (with CBZ)	9.13			0.948	0.807-1.096
		17 (w/o CBZ)	8.33	1.096	1.013-1.186	0.798	0.694-0.917
2	AUCss	9 (w/o CBZ)	83.25				
		17 (with CBZ)	84.16	1.011	0.960-1.065		
	Cmax	9 (w/o CBZ)	9.71				
		17 (with CBZ)	10.44	1.075	0.098-1.170		

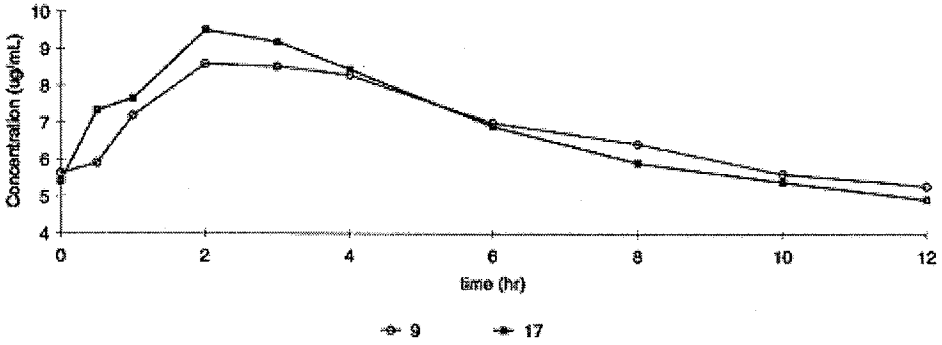
In Group 1, the co-administration of SPM 927 with carbamazepine (Day 9) led to slightly higher concentration-time curves than the administration of SPM 927 alone. The treatment ratio of the pharmacokinetic parameters was estimated at 107.9 % based on the AUC and at 109.6 % for Cmax .The 90%- confidence intervals for these ratios were within the bioequivalence ranges: 100 to 116% for AUC and 101 to 119% for Cmax, respectively. This can be seen in the following Figure, where Day 9 in the profile is for the coadministration Day.

Geometric Mean SPM 927 Concentration Profiles of Days 9 and 17 for Group 1



In group 2, these differences were lower. The treatment ratio (co-administration vs SPM 927 alone) of AUC was 101.1% and of C, 107.5%. The 90% confidence interval of these ratios were in 96 t0 107% and 99 to 117%, respectively. The geometric mean profile for Day 9 and 17 in Group 2 are given below.

Geometric Mean SPM 927 concentration profiles on Days 9 and 17 for Group 2



These results demonstrate that there is no effect of carbamazepine on the pharmacokinetics of SPM 927.

Although there are minor differences in group 1 and 2 at steady state, but these differences are minor

Pharmacodynamics:

The peak saccadic velocity (PSV), that is the maximum velocity of eye movement in terms of degree per second, was selected to be the primary parameter for the measurement of an influence of SPM 927 and/or carbamazepine on the eye motility, as an indicator of possible CNS-effects.

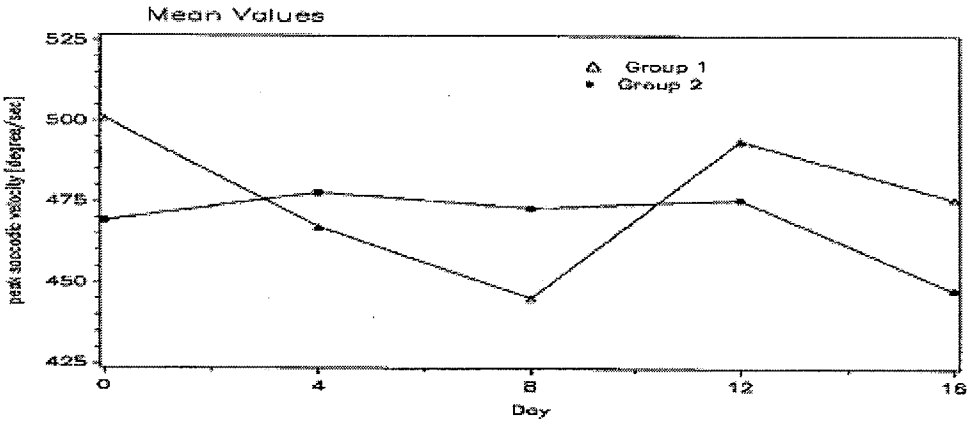
In Group 1, receiving carbamazepine from Days 2 – 9 and SPM 927 from Day 1 to Day 17, a maximum mean decrease of 11% on Day 8 was observed. After stopping the carbamazepine administration, the mean PSV increased again to the range of the baseline values.

In Group 2, receiving carbamazepine on Days 10 – 17 and SPM 927 from Day 1 to Day 17, the PSV profile was different. Up to Day 12 (corresponding to Day 4 for Group 1) the mean PSV remained unchanged at the baseline level. A decrease by 5.6% was observed on Day 16 (corresponding to Day 8 for Group 1).

Saccadic Eye Movements – Peak Saccadic Velocity [°/sec] Mean and Standard Deviation (SD)

Group	Day	N	Mean	SD
1	0	10	501	60
	4	10	467	69
	8	10	445	71
	12	10	494	65
	16	10	476	62
2	0	9	469	54
	4	9	478	59
	8	9	473	48
	12	9	476	57
	16	9	448	57

Figure: Mean SEM peak saccadic velocity [°/sec]



The following table shows the mean changes from baseline (Day 0) PSV values, probabilities of these values being statistically significant, as well as 95% confidence intervals (absolute values and percentage relative to the mean change from baseline).

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ON ORIGINAL

Table: Saccadic Eye Movements – Peak Saccadic Velocity- Statistical summary

	change from baseline	p	lower 95% conf.-int.	upper 95% conf.-int.	lower (% of change)	upper (% of change)
			GROUP=1			
Day 16 - Day 0	-24.9	0.3657	-79.8	30.0	-320	120
Day 12 - Day 0	-7.0	0.8034	-63.1	49.1	-904	704
Day 8 - Day 0	-55.5	0.0638	-114.4	3.3	-206	6
Day 4 - Day 0	-33.6	0.2510	-91.7	24.6	-273	73
			GROUP=2			
Day 16 - Day 0	-21.5	0.4163	-74.5	31.5	-346	146
Day 12 - Day 0	6.3	0.8113	-46.6	59.2	-741	941
Day 8 - Day 0	3.7	0.8776	-45.1	52.6	-1204	1404
Day 4 - Day 0	8.6	0.7493	-45.2	62.3	-528	728

The decrease of the peak saccadic velocity was observed at Day 4, after 4 days of repeated administration of SPM 927 and 2 days of co-administration of carbamazepine. The highest decrease was observed on Day 8. The change from the baseline value on this day showed no significance (p=0.06) like all other changes.

SPM 927 alone at a dose of 200 mg twice daily did not influence this parameter significantly. The effect of the combination of SPM 927 and carbamazepine was less pronounced when the carbamazepine treatment was set up after SPM 927 was already at steady state for approximately 6 days.

Safety:
According to the sponsor, no serious or life-threatening adverse events were observed during this trial and none of the subjects was withdrawn due to adverse events.

In total 16 non-serious adverse events occurred. The most frequently reported and expected adverse event was fatigue, observed three times after administration of SPM 927 alone and once after co-administration. All adverse events were of mild intensity and all subjects had recovered by the end of the trial.

Conclusion:

- Co-administration of carbamazepine had no influence on the steady state pharmacokinetics of SPM 927: Pharmacokinetic parameters AUC, Cmax and t1/2 of SPM 927 remained unchanged.

- SPM 927 did not influence the peak saccadic velocity significantly. The co-administration of SPM 927 and carbamazepine caused a small non significant decrease and this effect was less pronounced when the carbamazepine treatment was set up after SPM 927 was already at steady state for approximately 6 days.

APPENDIX II

OCPB FILING REVIEW

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N22-253, N22-254	**Brand Name**	NA
OCP Division (I, II, III)	DCP-I	**Generic Name**	Lacosamide (SPM 927, harkoseride and ADD 234037)
Medical Division	HFD-120	**Drug Class**	Antiepileptic
OCP Reviewer	Veneeta Tandon	**Indication(s)**	treatment of partial-onset seizures in patients with epilepsy aged 16 years and older
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Tablet: 50, 150, 200, 250 and 300 mg solution for infusion: 10 mg/mL b(4)
		Dosing Regimen	Starting dose: 100 mg/day given as BID Weekly increments of 100 mg/day Maintenance dose 200-400 mg/day, not to exceed mg/day b(4) Switch to IV: equivalent dose to oral
Date of Submission	9/28/07	**Route of Administration**	Oral and IV
Estimated Due Date of OCP Review	5/19/08	**Sponsor**	Schwarz Pharma
PDUFA Due Date	7/28/08	**Priority Classification**	Standard
Division Due Date	6/5/08		

Clin. Pharm. and Biopharm. Information

The sponsor has submitted — NDAs for Lacosamide for — different dosage forms. The Tablet NDA is indicated for both epilepsy and neuropathic pain. The injection formulation are indicated only for epilepsy indication. b(4)

The NDAs for epilepsy consists of three pivotal clinical trials (SP667, SP754, SP755) with the tablets and one replacement study with the IV solution (SP616). In addition to these there are four uncontrolled trials with the tablet and one with the IV solution b(4)

Note: For IV studies the lowest age studied is 18 years.

This filing review pertains to oral studies that the specific for the epilepsy indication.Refer to Tayo Fadiran's filing memo for N— for Filing details of the rest of this NDA.

Studies for Tablet: b(4)

1) Four drug interaction studies have been conducted with antiepileptics using the tablet formulation (effect of lacosamide on valproic and vice versa, effect of lacosamide on carbamazepine and vice versa): (SP601, SP602, SP603, SP618). No interaction observed.

Note: The four drug interaction studies are done with the capsule dosage form. Dose proportionality studies are also done with capsule. Biowaiver based on BCS Class I is requested for capsule and tablet BE study. Biowaiver also requested between tablet and commercial tablet.

2) Other antiepileptics evaluated in population analysis of Phase 3 studies (SP667, SP754, SP755): antiepileptics evaluated are: CBZ, OxCBZ, Lamotrigine, levetiractam, phenytoin, phenobarbital, topiramate, valproate, zonisamide.: No interaction observed.
3) PK in patients with epilepsy evaluated in population analysis of Phase 3 studies (SP754, SP755): PK not different in patients
4) PK-PD modeling in seizure patients pooled from all three studies: Support the proposed dosing regimen

Note: Individual population PK report has been provided for each of the three clinical efficacy studies. Pooled population analysis has not been conducted.

Studies for IV solution for injection:

1) Clinical safety, PK and tolerability study with 10, 15 and 30 minute infusions up to 5 days (SP757): confirmed comparability of IV and oral
2) Safety and PK of IV as replacement of oral lacosamide at doses 200-600 mg/day with 30 or 60 minute infusions up to 2 days (SP616): confirmed comparability of IV and oral
3) Two BE studies comparing IV solution (different infusion rates: 15, 30 and 60 minutes) to tablets at a 200 mg dose (SP658 and SP645) : 30 and 60 minutes were BE but 15 minute infusion failed Cmax (90% CI was 1.04-1.38)
4) Comparing IV solution to tablet in poor and extensive metabolizers of CYP 2C19 to look for metabolic differences in the two routes of administrations with 200 mg SD and 200 mg BID dose for 4.5 days (infusion of 60 minutes): (SP643): Not different, sample size is small
5) PK and safety of ascending IV doses 50-300 mg: (SP834): Dose proportional in this range.
6) Mass balance following oral and IV of 1 hour infusion (SP619): Similar between the two routes. This will be reviewed by Tayo.

Commercial formulation was used in Phase 1, 2 and 3 studies.

Note: Label states that [redacted] b(4)

[redacted] b(4)

The sponsor has provided the Clinical Pharmacology and Biopharmaceutics summary template as requested, but this document only has hyperlinks to the text in other modules, actual text is not provided here.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	2	2	PK and safety with IV
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	ascending IV doses 50-300mg
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	valproic acid and carbamazepine
In-vivo effects of primary drug:	X	2	2	valproic acid and carbamazepine
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	X	1	1	
Population Analyses -				
Data rich:				
Data sparse:	X	3		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4	4	1 1 1 b(4) 2) 200 mg tablet vs. IV (30 and 60 minutes infusion) 3) 200 mg tablet vs. IV (15 minutes infusion) 4) comparing IV solution to tablet in PM and EM for CYP2C19 The IV studies have used the commercial formulation, but highest dose is not used in the BE study. Higher doses are used in a clinical safety and PK study. PK is also linear
Bioequivalence studies -				/ / / b(4)
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS	X			/ / / b(4
BCS class	**X**			
III. Other CPB Studies	-			
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			
Literature References	-			
Total Number of Studies	**11 PK + 3 Pop PK+ 1 PK-PD + 2 assay reports**	**11 PK + 3 Pop PK+ 1 PK-PD + 2 assay reports**		

Filability and QBR comments		
I.	**"X" if yes**	Comments
II. Application filable?	Yes	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
III. Comments sent to firm? **IV.**		See below for comments
QBR questions (key issues to be considered)	• Is the dosing regimen appropriate based on dose response relationship and AE profile • Are there any significant drug interactions with other AEDs? • Is the PK similar between patients and healthy subjects? • Is the IV injectable bioequivalent to the oral and are the infusion rates recommended adequate based on BE studies? / ((/	b(4)
Other comments or information not included above	Biowaiver requests will be reviewed by the ONDQA.	
Primary reviewer Signature and Date	Veneeta Tandon	
Secondary reviewer Signature and Date	Ramana Uppoor	

Comments to the sponsor:

- Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given.

- The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.

- Please submit the applicable data from the following to support ALL population PK analyses and concentration-response relationship analyses:
    - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
    - A model development decision tree and/or table which gives an overview of modeling steps.
    - For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

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

/s/

Veneeta Tandon
6/9/2008 01:32:35 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
6/9/2008 06:56:19 PM
BIOPHARMACEUTICS
This review represents the integrated opinion/recommendation of the Office of Clinical Pharmacology for the 'partial seizures' indication. Dr. Mehta will be final signatory because this has a phase 4 commitment request.

Mehul Mehta
6/10/2008 10:46:28 AM
BIOPHARMACEUTICS

PHARMACOMETRIC REVIEW

NDA:	22253, 22254, [redacted] b(4)
Drug name:	Lacosamide
Indication:	For 22253 (Lacosamide Tablets): For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older. For [redacted] b(4) For the management of neuropathic pain associated with diabetic peripheral neuropathy
Proposed Regimen (Sponsor):	For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older: • Initially, 100 mg/day (BID). The dose may be increased, based on clinical response and tolerability, at weekly intervals by 100 mg/day to a daily dose of 100 mg/day to 400 mg/day. The maximum dose should not exceed [redacted] mg/day. b(4) Lacosamide injection may be given without further dilution or mixed in compatible diluent and should be administered intravenously over at least [redacted] minutes. b(4) For the management of neuropathic pain associated with diabetic peripheral neuropathy:

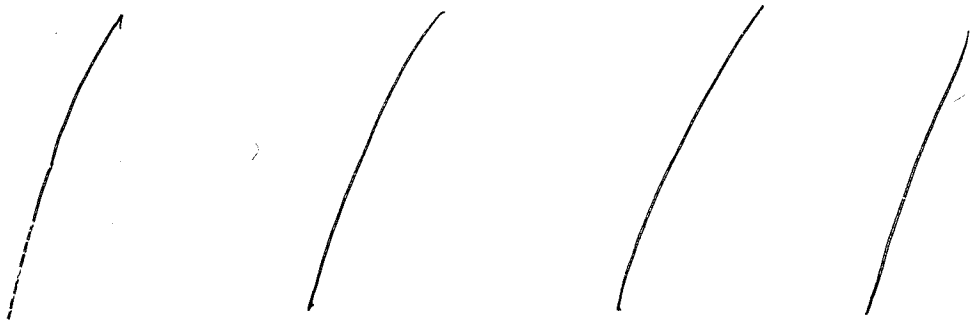
	mg/day.
Applicant:	Schwarz Pharma, Inc.
OCP Reviewer	Neurology Products OCP Reviewer: Veneeta Tandon, Ph.D. Anesthesia, Analgesia, and Rheumatology Products OCP Reviewer: Emmanuel Fadiran, Ph.D. Lei Zhang, Ph.D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	NDA
Submission Date:	09/28/2007
PDUFA Date:	07/28/2008

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

The review is focused on the lacosamide exposure-response analyses in patients with partial seizure and in patients with distal diabetic neuropathy. These findings support approval related and labeling decisions (depending on the indication).

Diabetic Nephropathy: Across the pivotal trials, there are considerable number of drop-outs due to AEs (caused by higher doses/exposures) rendering these trials un-interpretable. Based on observations from



b(4)

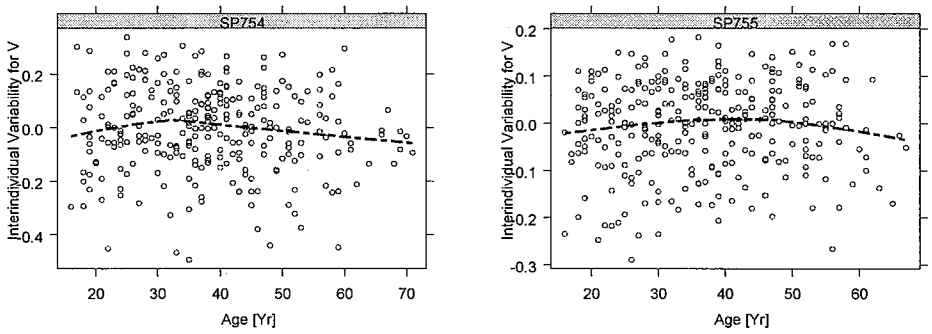
Partial Seizure: Based on observations from 3 pivotal effectiveness trials (Study SP667, SP754, and SP755), exposure-effectiveness relationship is demonstrated in responder patients with partial seizure by the end of titration phase and by the end of maintenance phase. Because the response curve becomes flat beyond the median exposure of 400 mg dose, 600 mg dose does not appear to provide additional benefit compared to 400 mg dose.

2 QUESTION BASED REVIEW

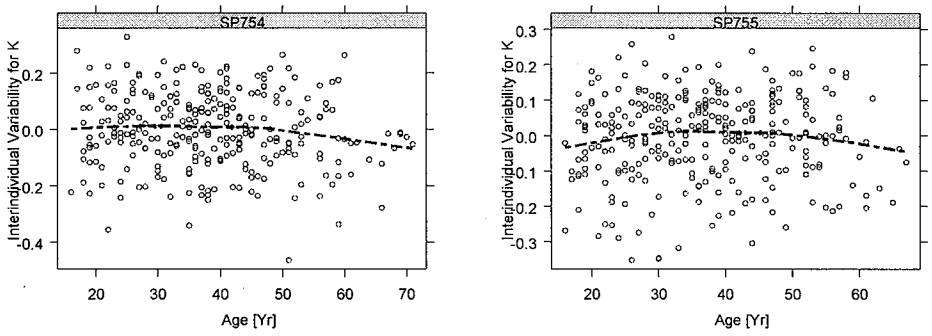
1. Is there any age and gender effect in patients with partial seizure based on population PK analysis?

Age and sex do not influence exposure in patients with partial seizure based on population PK analyses results. The Population PK analyses are performed using sparse PK sampling taken from two pivotal clinical effectiveness trials (SP754 and SP755). The difference between individual and population mean parameter (called as inter-individual variability) for volume of distribution and clearance versus age and gender are presented in Figure 1 and Figure 2. No specific trend can be identified.

Figure 1 Interindividual Variabilities for Vc and Ke versus Age

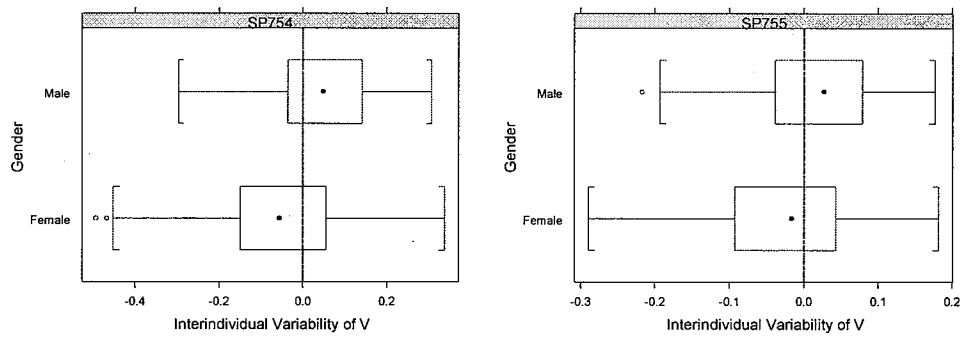


(A). IIV on V ~ Age for Study SP754 and SP755

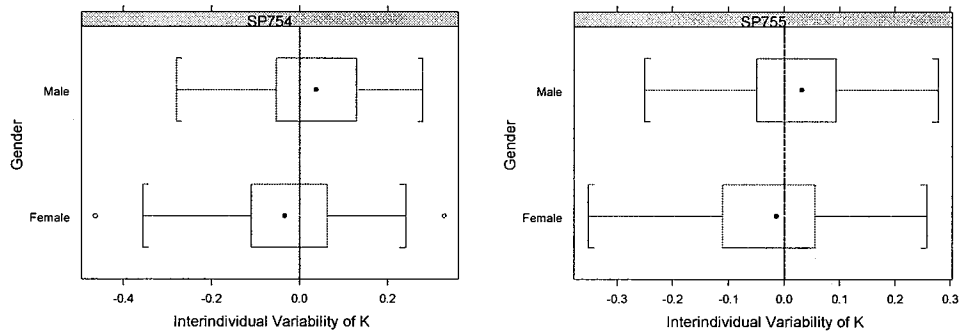


(B) IIV on Ke ~ Age for Study SP754 and SP755

Figure 2 Interindividual Variabilities for Vc and Ke versus Gender



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



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

2. What are the characteristics of exposure/effectiveness relationships for lacosamide in treating patients with partial seizure?

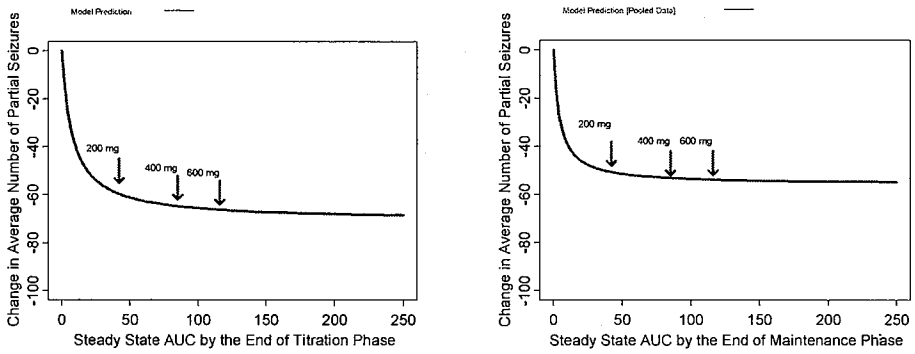
The exposure-response relationship for lacosamide in treating patients with partial seizure is established in the responder patient population based on clinical observations in 3 clinical effectiveness studies (SP667, SP754, and SP755). Subjects with no evaluable slope for the baseline phase, or R^2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

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

An Emax model is applied to describe the exposure-effectiveness relationship by using nonlinear least square regression. The model fitted curves are presented in Figure 3. The response curve started to flatten out beyond the median exposure of 400 mg dose based

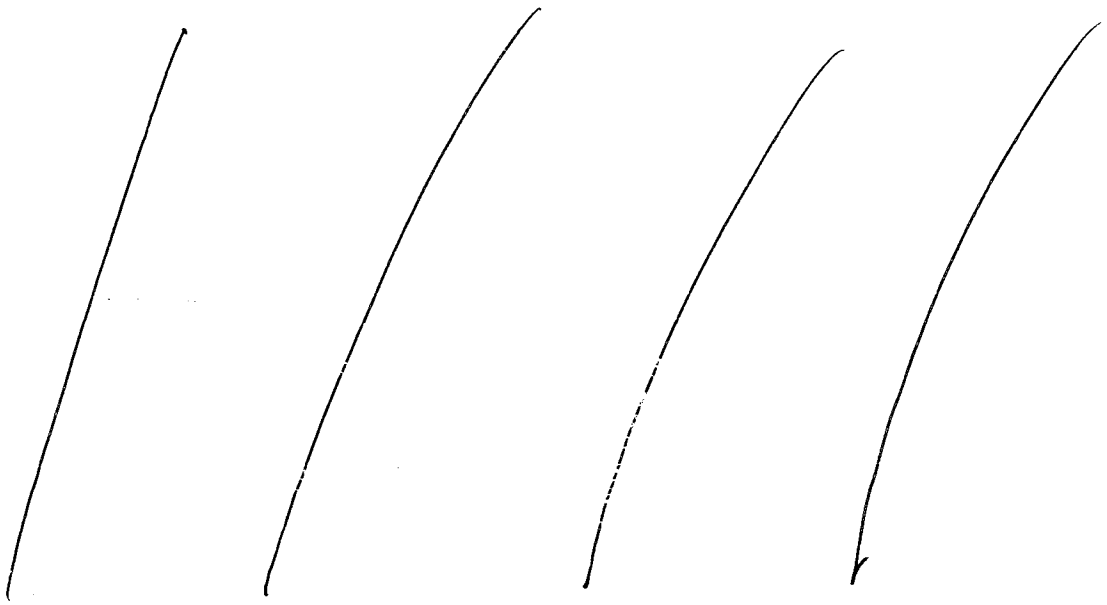
on the observed exposure-response relationship. Therefore, 600 mg dose does not appear to provide additional benefit compared to 400 mg dose.

Figure 3 Exposure-Response Relationship for Lacosamide in Treating Patients with Partial Seizure by the End of Titration Phase (A) and by the End of Maintenance Phase (B) (Responder's Analysis).



(A) (B)

3. What are the characteristics of exposure-effectiveness relationship for lacosamide in treating patients with painful distal diabetic neuropathy?



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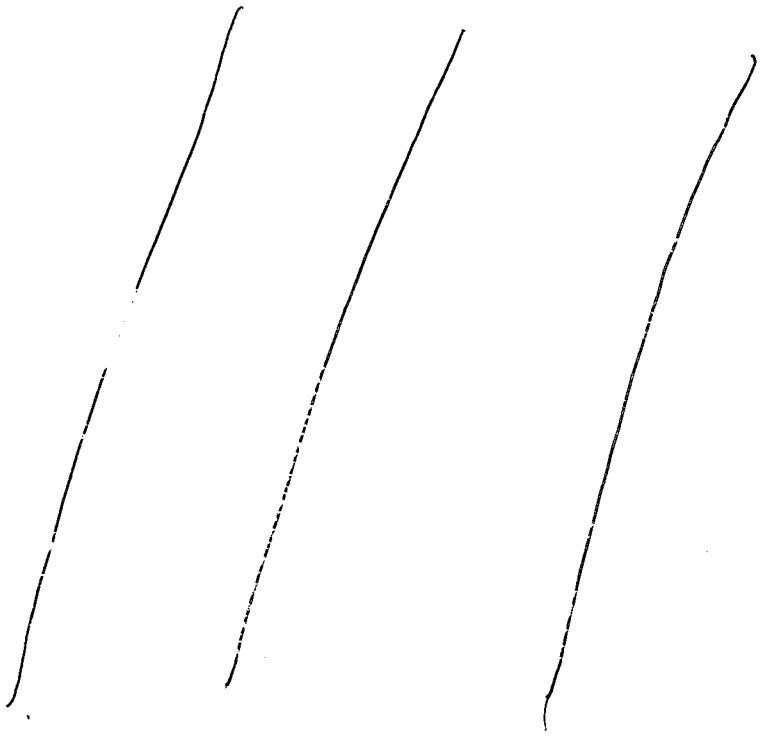

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4. Dose concurrent administration of carbamazepine, phenobarbital, or phenotyoin affect pharmacokinetics of lacosamide in patients with partial onset of seizure, based on population PK results?

No clinically meaningful change in pharmacokinetics of lacosamide was observed when lacosamide was coadministrated with carbamazepine, phenobarbital, or phenotyoin based on population PK results.

The sponsor indicates in the label that based on the population PK results, lacosamde exposure is reduced when lacosamide is coadministered with carbamazepine, phenobarbital, or phenotyoin. In the population PK analysis, the sponsor used three covariates corresponding to the three above mentioned drugs in which the values were assigned as 1 when these drugs were used alone or in combination with 1or 2 other drugs in lacosamide treated patients. The sponsor demonstrated that inclusion of these covariates lead to significant improvement in describing the lacosamide pharmacokinetic variability.

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

Mechanistic potential for drug-drug interaction between lacosamide and carbamazepine, phenobarbital, or phenotyoin is unclear. About 40% of parent lacosamide is excreted through kidney, suggesting involvement of metabolism in the elimination of the other 60% of the drug. Lacosamide has been shown to be a 2C19 substrate. Carbamazepine is a known 2C19 inducer. However, phenotyoin and phenobarbital are not known 2C19 inducers. These 3 drugs are CYP3A inducers. Whether the data imply that CYP3A may be involved in the metabolism of lacosamide is unclear.

Assuming drug-drug interaction exists between lacosamide and carbamazepine, phenobarbital, or phenotyoin. Based on the population PK analysis results, including the drug-drug interaction covariate effect identified for these three drugs, about 20% reduction in lacosamide exposure might be expected at worst, which is not clinically meaningful.

2.1 BACKGROUND

Lacosamide (LCM) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. Electrophysiological studies have shown that LCM enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces hyperexcitability of neurons characteristic for both epilepsy and neuropathic pain. This is a novel mode of action since other sodium channel modulators such as lamotrigine, phenytoin, and carbamazepine enhance fast inactivation with no or small effects on slow inactivation. In addition, it has been shown that LCM interacts with collapsing response mediator protein 2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth. The interaction of LCM with CRMP-2

represents a second mode of action of LCM and this may potentially underlie sustained disease-modifying effects.

This submission is a New Drug Application (NDA) to obtain marketing approval for the indication of the treatment of epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older and for the management of neuropathic pain associated with diabetic peripheral neuropathy

2.2 STUDIES

2.2.1 Clinical Studies in Patients with Partial Onset Seizure

The sponsor performed 3 major efficacy trials, including Study SP667, Study SP754, and Study SP755, to determine the indication of the treatment of epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older.

Study SP 667

Study 667 is a phase IIb, multicenter, double-blind, randomized, placebo-controlled, parallel group trial to investigate the efficacy and safety of SPM 927 (200mg/day, 400mg/day, 600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization The primary objective of this trial was to evaluate the efficacy of SPM 927 administered concomitantly with 1 or 2 antiepileptic drugs (AEDs) in subjects with or without additional vagus nerve stimulation (VNS) who currently have uncontrolled partial seizures with or without secondary generalization. The secondary objectives were to evaluate the safety of SPM 927 and the dose response relationship of SPM 927 with regards to efficacy and safety and to examine steady-state plasma concentrations of SPM 927 and concomitant AEDs during oral administration.

Patients were enrolled into one of the sixty-eight (68) trial sites in the United States, Hungary, Lithuania, Poland, Germany, Sweden, Switzerland, and United Kingdom. Diagnosis of partial seizures was based on the 1981 criteria of the International League Against Epilepsy for international classification of epileptic seizures. Subjects having any of the following three partial seizure subtypes were eligible for inclusion in this trial:

- Simple partial seizures with motor signs (consciousness unimpaired)
- Complex partial seizures (consciousness impaired)
- Partial seizures evolving into secondarily generalized seizures

Subjects were observed to have partial onset seizures for at least the last two years despite prior therapy with at least 2 AEDs. Included subjects reported at least 4 partial onset seizures per 28 days on the average, with seizure-free period no longer than 21 days, in the 4-week period prior to entry into the baseline period. Subjects were on a stable dosage regimen of a maximum of 2 AEDs, with or without additional concurrent stable VNS. The dosage of concomitant AED therapy was kept constant for at least 4 weeks prior to entry into the baseline period. A total of 542 subjects were screened for this trial. A total of 497 subjects were enrolled in the trial. Of the 497 enrolled subjects, 421 were randomized and received at least one dose of trial medication. Because of audit

findings suggesting noncompliance with the protocol, all subjects at Site 12 (n=3) were removed from the analysis sets. As a result, only 418 subjects were included in the safety analysis. A total of 415 of these subjects also had at least one post-baseline efficacy assessment and were included in the efficacy analysis

Dose titration began at 100mg/day or placebo. Trial medication was administered in 2 equal oral doses per day at 12-hour intervals (4 tablets in the morning and 4 tablets in the evening). Subjects were titrated to the target dose by 100mg/day per week.
Subjects randomized to 600mg/day were titrated by 100mg/day per week for 6 weeks to 600mg/day. Subjects randomized to 400mg/day received placebo during Weeks 1 and 2 and titrated by 100mg/day per week during Weeks 3 through 6 to 400mg/day. Subjects randomized to 200mg/day received placebo during Weeks 1 through 4 and titrated by100mg/day per week during Weeks 5 and 6 to 200mg/day. One back-titration of 100mg/day was allowed at the end of the Titration Phase in cases of intolerability. Subjects who were not able to tolerate the trial medication at an earlier time point during titration or who were not able to tolerate the reduced dose, were tapered off trial medication and withdrawn from the trial. Once the dose was reduced, it could not be increased later.

After the Titration Phase, subjects entered the 12-week Maintenance Phase on either their target dose or if 1 dose reduction step was performed, on the reduced dose. Subjects who required any additional dose reduction during the Maintenance Phase were tapered off trial medication and withdrawn from the trial. Subjects who completed the Maintenance Phase were given the opportunity to participate in an open-label extension trial of SPM 927 (SP615). Subjects who chose to enroll in the open-label extension trial were transitioned in a double-blind fashion from their maintenance dose to 200mg/day over a 2-week period. Subjects had a final clinic visit (Transition Visit 2) at the end of Week 2 of the Transition Phase. Subjects who did not complete the Maintenance Phase or who chose not to participate in the open-label extension trial were tapered off trial medication. The randomized dose was reduced in a double-blind fashion over a 3-week period by 200mg/day per week. Subjects had a final clinic visit (Taper Visit 2) at the end of Week 3 of the Taper Phase. The maximum duration of treatment was planned to be 21 weeks (147 days).

The assessment of efficacy was based on seizure frequency. Seizure counts were analyzed in 2 ways:
1. Reduction in seizure frequency per 4 weeks from Baseline to Maintenance Phase.
2. Response (improvement) to treatment of at least 50% from Baseline to Maintenance Phase.
For the Food and Drug Administration (FDA), reduction in seizure frequency (variable 1) was the primary efficacy variable and the responder rate (variable 2) was the secondary efficacy variable.

Study SP 754

Study 754 is a phase III, A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (400 and

600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization. The primary objective of this trial is to evaluate the efficacy of LCM administered concomitantly with 1, 2, or 3 antiepileptic drugs (AEDs) in subjects with or without additional vagal nerve stimulation (VNS) who currently have uncontrolled partial seizures with or without secondary generalization. The secondary objectives are to evaluate the safety of LCM, the dose-response relationship of LCM with regards to efficacy and safety, and to examine steady-state plasma concentrations of LCM and concomitant AEDs during oral administration of LCM.

This trial was conducted at 72 clinical centers enrolling subjects in the United States of America (USA). Diagnosis of partial seizures was based on the 1981 published criteria of the International League Against Epilepsy for international classification of epileptic seizures. Subjects having any of the following 3 partial seizures subtypes were eligible for inclusion in this trial:

- Simple partial seizures with motor signs (consciousness unimpaired)
- Complex partial seizures (consciousness impaired)
- Partial seizures evolving into secondary generalized seizures

Subjects were observed to have partial onset seizures for at least the last 2 years despite prior therapy with at least 2 AEDs (concurrently or sequentially) and were observed to have on the average at least 4 partial onset seizures per 28 days with seizure free phase no longer than 21 days in the 8 week period prior to entry into the Baseline Phase. Subjects were on a stable dosage regimen of at least 1 but no more than 3 AEDs, with or without additional concurrent stable VNS. The VNS must have been in place for at least 6 months prior to trial entry. The dosage of concomitant AED therapy and the settings of VNS must have been kept constant for a period of at least 4 weeks prior to entry into the Baseline Phase. A total of 556 subjects were screened for this trial. A total of 489 subjects were enrolled in the trial and comprised the ES; 54 subjects were screen failures and 13 additional subjects were excluded from the enrolled count due to not meeting all screening criteria although classified as Baseline Failures based on the trial termination case report form (CRF). Of the 489 enrolled subjects, 405 were randomized. All the 405 randomized subjects received at least 1 dose of trial medication and comprise the Safety Set (SS). A total of 402 subjects also had at least 1 post-Baseline efficacy assessment and are considered part of the full analysis set (FAS). Among the 402 subjects of the FAS, 280 subjects had at least 1 seizure frequency assessment collected during the Maintenance Phase and did not have any major protocol deviations and thus comprise the per-protocol set (PPS).

Subjects were enrolled and entered into an 8 week Baseline Phase. At the end of the Baseline Phase, eligible subjects were randomized (1:2:1) in a double-blind fashion to 1 of 3 treatment arms (placebo, LCM 400mg/day, or LCM 600mg/day). The duration of the trial was up to 29 weeks including an 8-week Baseline Phase and up to a 21-week Treatment Phase. The Treatment Phase was comprised of the following: 6 weeks forced titration up to the respective randomized dose of LCM or placebo (a 1-step back-titration of 100mg/day or placebo was allowed at the end of the Titration Phase), 12 weeks maintenance on the achieved randomized dose, and 2 weeks transition or 3 weeks taper.

The Transition Phase (bringing subjects to a dose of 200mg/day LCM) was required for subjects who completed the Maintenance Phase and who chose to enroll in an open-label extension trial of LCM. The Taper Phase was required for subjects who completed the trial and chose not to enroll in the open-label extension trial of LCM or who discontinued prior to the end of the Maintenance Phase. The maximum duration of treatment was 19 weeks.

The assessment of efficacy was based on partial seizure frequency. Seizure counts were analyzed in 2 ways:
1. Efficacy was determined by the change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase.
2. Efficacy was determined by the proportion of responders where a responder is a subject experiencing a 50% or greater reduction in partial seizure frequency from the Baseline Phase to the Maintenance Phase.
For the Food and Drug Administration (FDA), change in seizure frequency (variable 1) was the primary efficacy variable and the responder rate (variable 2) was the secondary efficacy variable.

Study SP 755

Study 755 is a phase III, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization. The primary objective of this trial was to evaluate the efficacy of lacosamide (LCM; also referred to as SPM 927) administered concomitantly with 1, 2, or 3 antiepileptic drugs (AEDs) in subjects with or without additional vagus nerve stimulation (VNS) who currently have uncontrolled partial seizures with or without secondary generalization. The secondary objectives were to evaluate the safety of LCM, the dose-response relationship of LCM with regards to efficacy and safety, and to examine steady-state plasma concentrations of LCM and concomitant AEDs during oral administration of LCM.

Seventy-seven sites were activated in 12 countries in Europe (Croatia, Czech Republic, France, Finland, Germany, Hungary, Lithuania, Poland, Russia, Sweden, Spain, and United Kingdom) and Australia. Diagnosis of partial seizures was based on the 1981 published criteria of the International League Against Epilepsy for international classification of epileptic seizures. Subjects having any of the following 3 partial seizures subtypes were eligible for inclusion in this trial:
- Simple partial seizures with motor signs (consciousness unimpaired)
- Complex partial seizures (consciousness impaired)
- Partial seizures evolving into secondary generalized seizures

Subjects were observed to have partial onset seizures for at least the last 2 years despite prior therapy with at least 2 AEDs (concurrently or sequentially) and were observed to have on the average at least 4 partial onset seizures per 28 days with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the Baseline Phase. Subjects were on a stable dosage regimen of at least 1 but no more than 3 AEDs, with or without additional concurrent stable VNS. The VNS must have been in place for at least

6 months prior to trial entry. The dosage of concomitant AED therapy and the settings of VNS must have been kept constant for a period of at least 4 weeks prior to entry into the Baseline Phase. A total of 546 subjects were enrolled in the trial and comprised the Enrolled Set; 32 subjects were screen failures and 6 subjects denoted as Baseline failures did not meet all Screening criteria and were excluded from the count of enrolled subjects. Of the 546 enrolled subjects, 485 were randomized. All of the 485 randomized subjects received at least 1 dose of trial medication and comprise the Safety Set. A total of 477 subjects also had at least 1 post-Baseline efficacy assessment and are considered part of the Full Analysis Set (FAS). Among the 477 subjects of the FAS, 399 subjects had at least 1 seizure frequency assessment collected during the Maintenance Phase and did not have any major protocol deviations and thus comprise the Per-Protocol Set.

The subjects were enrolled into an 8-week Baseline Phase. At the end of the Baseline Phase, subjects were randomized (1:1:1) in a double-blind fashion to 1 of the 3 treatment arms: placebo or LCM (200mg/day or 400mg/day). The duration of the trial was 26 weeks including an 8-week Baseline Phase and 18-week Treatment Phase. The Treatment Phase was comprised of the following: 4 weeks forced titration up to the respective randomized dose of LCM or placebo (a 1-step back-titration of 100mg/day LCM or placebo was allowed at the end of the Titration Phase), 12 weeks maintenance on the achieved randomized (or once back-titrated) dose, and 2 weeks transition or taper. The Transition Phase (bringing subjects to a dose of 200mg/day LCM) was required for subjects who completed the Maintenance Phase and who chose to enroll in an open-label extension trial of LCM. The Taper Phase was required for subjects who chose not to enroll in the open-label extension trial of LCM or who discontinued prior to the end of the Maintenance Phase.

The assessment of efficacy was based on partial seizure frequency. Seizure counts were analyzed in 2 ways:
1. Efficacy was determined by the change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase.
2. Efficacy was determined by the proportion of responders where a responder is a subject experiencing a 50% or greater reduction in partial seizure frequency from the Baseline Phase to the Maintenance Phase.

2.2.2 Clinical Studies in Patients with Diabetic Peripheral Neuropathy

The sponsor also performed 3 primary efficacy trials, including Study SP742, Study SP743, and Study SP768, to determine the indication of neuropathic pain associated with diabetic peripheral neuropathy. The studies were detailed as following:

Study SP742 (Phase II b):
Study 742 is a multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 200, 400, and 600mg/day SPM 927 in subjects with painful distal diabetic neuropathy. The primary objective of the trial was to investigate the efficacy of 200, 400, and 600mg/day of lacosamide compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Secondary objectives were to

investigate the effect of lacosamide on subjects' perception of pain, sleep, activity, and quality of life, as well as to investigate the pharmacokinetics and safety of lacosamide.

Patients were enrolled in one of the fifty three sites in United States of America. Subjects were male or female, 18 years of age or older. Subjects had symptoms of painful distal diabetic neuropathy for 6 months to 5 years and had a diagnosis of diabetes mellitus (Type I or Type II). Subjects had HbA1c levels <12% with optimized diabetic control (best effort to achieve best control) for at least 3 months prior to Visit 1 and also had at least moderate pain (average pain intensity during the 7 days prior to Visit 2 of ≥4 out of 10 on an 11 point Likert scale).
A total of 736 subjects were screened for this trial of which 496 subjects were enrolled. In all, 370 subjects were randomized and received at least 1 dose of trial medication (93 subjects in the placebo group, 93 subjects in the 200mg/day lacosamide (LCM)n group, 91 subjects in the 400mg/day LCM group, 93 subjects in the 600mg/day LCM group); these subjects comprised the Safety Set (SS). A total of 365 of the 370 randomized subjects also had at least 1 post-baseline pain score recorded in their diary and represented the Full Analysis Set (FAS). Of the 370 randomized subjects, 258 had at least 1 diary pain score recorded during the Maintenance Phase, and no major protocol deviations; these subjects comprised the Per Protocol Set (PPS). Two hundred and thirty-five subjects completed the Maintenance Phase and were included in the Completer Set (CS).

Subjects began the trial with a 2-week Run-In Phase to ensure eligibility and to collect baseline data. Eligible subjects were then randomized in a double-blind 1:1:1:1 randomization scheme to placebo or 200mg/day, 400mg/day, or 600mg/day of lacosamide respectively (starting at 100mg/day and titrating upwards over 6 weeks to 100mg/day at weekly intervals or until reaching maintenance dose). All subjects who completed the 6-week Titration Phase entered a 12-week Maintenance Phase, after which subjects either entered a 2-week Transition Phase (for subjects who elected to continue treatment in an open-label-trial) or a 1-week Taper Phase. The Taper Phase was followed by a 2-week Safety Follow-Up Phase.

Study SP743 (Phase III):
Study 743 is a multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day and 600mg/day SPM 927 in subject with painful distal diabetic neuropathy. The primary objective of the trial was to investigate the efficacy of 400mg/day and 600mg/day lacosamide compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Two titration schemes for the 400mg/day lacosamide dose were evaluated to determine if additional tolerability was achieved at a slower titration rate. Secondary objectives were to investigate the effect of lacosamide on subjects' perception of pain, sleep, activity, and quality of life, as well as to investigate the pharmacokinetics and safety of lacosamide.

Patients were enrolled in one of the fifty two sites in Belgium, the Czech Republic, Hungary, Italy, the Netherlands, Spain, Poland, Romania, Russia, Germany, France, and the United Kingdom. Subjects were male or female, 18 years of age or older. Subjects had clinically symptoms of painful distal diabetic neuropathy for 6 months to 5 years and

had a diagnosis of diabetes mellitus (Type I or Type II). Subjects had at least moderate pain (average pain intensity during the 7-day period prior to Visit 2 of ≥4 out of 10 on an 11-point Likert scale). Furthermore, subject had glycosylated hemoglobin (HbA_{1c}) levels <12% with optimized diabetic control (best effort to achieve best control) for at least 3 months prior to Visit 1.

A total of 513 subjects were screened for this trial from which a total of 411 subjects were enrolled and 357 subjects were randomized (74 in placebo, 150 in 400mg/day lacosamide [LCM], and133 in 600mg/day LCM). All subjects who were randomized also received at least 1 dose of trial medication and are referred to as the Safety Set (SS). A total of 355 subjects in the SS had at least 1 post-Baseline diary pain score and were considered part of the Full Analysis Set (FAS). A total of 265 subjects in the FAS had at least 1 post-Baseline diary pain score from the Maintenance Phase and did not have any major protocol deviations and were considered part of the Per Protocol Set (PPS). Two hundred and forty-seven subjects in the FAS completed the 12-week Maintenance Phase and were part of the Completers Set (CS).

Baseline data were collected during the second week of a 2-week Run-In Phase to ensure subject eligibility. Eligible subjects were then randomized to receive a maximum of 400 or 600mg/day lacosamide (subjects had their dose titrated to randomized dose during a 6-week Titration Phase) or placebo. During the 6-week Titration Phase, subjects had their dosage escalated by 100mg/day weekly increments from a beginning dosage of 100mg/day to a maximum dosage of 400 or 600mg/day. The 2 400mg/day titration schemes differed in the rate of dose escalation; the first scheme had the subjects on 100mg/day for the first 3 weeks of the Titration Phase prior to dose escalation and the second scheme had the subjects escalate to the target dose (400mg/day) over the first 4 weeks then undergo sham titration for the remaining 2 weeks of the Titration Phase. The highest attained dose was maintained for 12 weeks, after which the subjects either entered a 2-week Transition Phase (for subjects who elected to continue treatment in an open-label trial) or a 1-week Taper Phase. The Taper Phase was followed by a 2-week Safety Follow-Up Phase.

Study SP768 (Phase III):

Study 768 is a multi-center, randomized, double-blind, placebo controlled, parallel-group trial to assess the efficacy and safety of SPM 927 (200, 400, and 600mg/day) in subjects with painful distal diabetic neuropathy. The primary objective of the trial is to investigate the efficacy of 200, 400, and 600mg/day of SPM 929 compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Secondary objectives are to investigate the effect of SPM 929 on subjects' perception of pain, sleep, activity, quality of life, mood, and other pharmacoeconomic indicators, as well as to investigate the pharmacokinetics and safety of SPM 929.

Patients were enrolled in one of the eighty-four sites in the United States of America. Subjects were male or female, 18 years of age or older. Subjects had symptoms of painful distal diabetic neuropathy for 6 months to 5 years and had a diagnosis of diabetes

mellitus (Type I or Type II). Subjects had HbA_{1c} levels <12% with optimized diabetic control (best effort to achieve best control) for at least 3 months prior to Visit 1 and also had at least moderate pain (average pain intensity during the 7 days prior to Visit 2 of ≥4 out of 10 on an 11-point Likert pain scale).

A total of 1222 subjects were screened for this trial; 570 (46.6%) were screen failures and 654 subjects were enrolled and comprised the Enrolled Set (ES). Of the ES, 183 (28.0%) were run-in failures leaving 469 randomized subjects of which 468 received at least 1 dose of trial medication and were included in the Safety Set (SS). A total of 453 subjects also had at least 1 post-baseline pain score recorded in their diary and were included in the Full Analysis Set (FAS). Of the 453 subjects in the FAS, 313 had at least 1 diary pain score recorded during the Maintenance Phase and did not have any major protocol deviations and were included in the PPS. 262 subjects from the FAS completed the Maintenance Phase and were included in the Completer Set (CS).

Subjects began the trial with a 2-week Run-In Phase to ensure eligibility and to collect Baseline data. Eligible subjects were then randomized in a double-blind 1:2:2:2 randomization scheme to placebo or 200mg/day, 400mg/day, or 600mg/day of lacosamide respectively (starting at 100mg/day and titrating upwards over 6 weeks to 100mg/day at weekly intervals or until reaching maintenance dose). All subjects who completed the 6-week Titration Phase entered a 12-week Maintenance Phase, after which subjects either entered a 2 week Transition Phase (for subjects who elected to continue treatment in an open-label trial) or a 1-week Taper Phase. The Taper Phase was followed by a 2-week Safety Follow-Up Phase.

2.3 AIM OF ANALYSIS

The aim for the population PK analysis was to describe the pharmacokinetics of Lacosamide in healthy subjects, patients with partial onset seizure, and patients with diabetic peripheral neuropathy and to identify the source of interindividual variability in the pharmacokinetics of Lacosamide. Furthermore, the exposure-response relationships for effectiveness were to be investigated. Based on the exposure-response analyses results, the appropriate dose was also evaluated.

3 SPONSOR'S ANALYSIS

3.1 SUMMARUY OF SPONSOR'S POPULATION PK AND EXPOSURE-RESPONSE ANALYSES

The sponsor submitted 2 population PK reports for healthy subjects, 2 population PK reports for patients with partial seizure, 3 population PK reports for patients with diabetic neuropathy, and 2 exposure-response analyses reports. They were summarized in Table 1.

Table 1 Summary of Population PK and Exposure-Response Analyses Study Reports

Type	Study Number	Report	Population
Pop-PK	SP-640	Population Pharmacokinetics of Lacosamide in Healthy Male and Female Subjects	Healthy Subjects
	SP-620	Population Pharmacokinetics of Lacosamide in Healthy Subjects with Different Age and Gender	
	SP-755	Population Pharmacokinetics of Lacosamide in Subjects with Partial Seizures with or without Secondary Generalization	Partial Seizure
	SP-754	Population Pharmacokinetics of Lacosamide in Subjects with Partial Seizures with or without Secondary Generalization	
	SP-665	Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy	Diabetic Neuropathy
	SP-742	Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy	
	SP-743	Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy	
E-R	SPM-927	The pharmacokinetic-pharmcodynamic (PK-PD) analysis of lacosamide in subjects with partial onset seizures based on data collected from trials SP667, SP754, and SP755 was described in study report SPM927	Partial Seizure
	SPM-929	Parhamcokinetic-pharmacodynamic modeling of lacosamide in subjects with painful distal diabetic neuropathy	Diabetic Neuropathy

3.2 INDIVIDUAL POPULATION PK REPORTS

The sponsor submitted 7 population PK analyses reports, including 2 reports for healthy subjects, 2 reports for patients with partial seizure, and 3 reports for patients with diabetic neuropathy.

3.2.1 Population PK results in healthy subjects

The sponsor submitted 2 population PK analysis reports for healthy subjects. They were summarized as following:

3.2.1.1 Population Pharmacokinetics of Lacosamide in Healthy Male and Female Subjects, Trial Number SP-640

5.3.1.1.1 OBJECTIVES:

Objectives of the population PK analysis were the following:

1. To describe population PK characteristics (=typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in healthy male and female subjects.
2. To quantify the relationship between different subject-specific factors (=possible covariates, e.g., body weight, creatinine clearance) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [k_e]).
3. Estimation of the magnitude of residual variability that cannot be described by the population PK model in these subjects.

Based on these results, important information about the pharmacokinetics of LCM after administration of high dosages (400 and 800mg/day) compared to the dosages administered in other Phase 1 trials and about the differences in the pharmacokinetics of LCM in male and female subjects should be gained.

5.3.1.1.2 CLINICAL STUDY OVERVIEW:
The population PK analysis was based on the PK observations from trial SP640.

SP640 was a Phase 1, double-blind, single-site, randomized, placebo- and positive-controlled, parallel-design trial with multiple oral dose administration of LCM, moxifloxacin, or placebo (thorough QT trial). Healthy male and female subjects had 6 days of treatment with 400 or 800mg/day LCM or placebo, or 3 days of treatment with 400mg/day moxifloxacin respectively. A total of 247 subjects were randomized: 60 subjects in the LCM 400mg/day group, 71 subjects in the LCM 800mg/day group, 62 subjects in the placebo group, and 54 subjects in the moxifloxacin group. The Treatment Phase consisted of treatment with 400mg/day (200mg bid) or 800mg/day (400mg bid) LCM or placebo daily on Days 1 to 6, or 400mg moxifloxacin once daily on Days 1 to 3. 220 (89.1%) of the 247 randomized subjects completed the trial. Almost all subjects (24/27 subjects, 89%) who discontinued from the trial were female (placebo group: 4 subjects, 400mg/day group: 3 subjects, 800mg/day group: 17 subjects); the 3 male subjects who discontinued from the trial were all in the placebo group. Plasma samples for determination of LCM and SPM 12809 concentrations and PK analysis were drawn on Day 3 prior to the morning dose (0 hour), 2 hours after the morning dose, and prior to the evening dose (12 hours); Day 5 prior to the morning dose (0 hour) and prior to the evening dose (12 hours); and Day 6 prior to the morning dose and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the morning dose for all subjects in the LCM 400mg/day, LCM 800mg/day and placebo group. The sponsor performed non-compartmental analysis to obtain pharmacokinetic parameters. In the mean time, they performed population PK analysis by using the same PK data.

5.3.1.213 DATA FOR ANALYSIS:
The population PK evaluation was performed based on 1701 LCM plasma concentrations from 123 subjects (with a median of 15 samples per subject), with exclusion of the following data. Plasma samples from all placebo and SPM 12809 records were excluded. All 15 plasma concentrations of LCM from Subject 81064 were excluded, because the subject apparently missed dosing at morning of Day 6. Therefore subject 81064 was classified as major deviator and was excluded from the PK set in the CTR for SP640.

Analysis of plasma samples was performed with a validated liquid chromatography/mass spectrometry (LC/MS) method with the lower limit of quantification (LOQ) for LCM was 0.1 µg/mL.

The following parameters were used in the evaluation of possible covariates: Age, Sex (Sex=0 for males, Sex=1 for females), Height (HGT), Body weight (BW), Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CL_{cr}), Alkaline phosphatase (AP), Gamma-glutamyltransferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin.

Where LBW and CLcr were calculated by using the following equations,

$$\text{LBW [kg] in males} = 1.10 \times \text{weight[kg]} - 0.0128 \times \text{BMI} \times \text{weight[kg]}$$

$$\text{LBW [kg] in females} = 1.07 \times \text{weight[kg]} - 0.0148 \times \text{BMI} \times \text{weight[kg]}$$

and

$$CL_{cr}[mL/\min] = \frac{(140 - age) \times weight[kg]}{72 - S_{creat}[mg/mL]}$$

If sex=female then $CL_{cr} = CL_{cr} \times 0.85$

5.3.1.1.4 METHODS:

A one-compartment model with first-order absorption and firs-order elimination (ADVAN2) was used (chosen from prior knowledge) for the population PK evaluation of LCM by using first order method (FO) in NONMEM Version IV (NONMEM Project Group, University of California, San Francisco, US)

Model selection was based on a global measure of goodness-of-fit of a model, the objective function (OBF) in NONMEM (= - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

- Observed concentrations vs. individual predicted concentrations (DV vs. IPRE)
- Observed concentrations vs. predicted concentrations (DV vs. PRED)
- Weighted residuals vs. predicted concentrations (WRES vs. PRED)
- Residuals vs. predicted concentrations (RES vs. PRED)
- Residuals vs. time (RES vs. time)
- Predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
- Weighted residuals vs. time (WRES vs. time)
- Individual predicted concentrations and measured concentrations vs. time (IPRE/DV vs. time)

The following criteria were used as additional criteria:

- Reduction of inter- and/or intra-individual (=residual) variability
- Reduction of the standard errors with respect to parameter estimates

- Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

- A "successful minimization" statement by the NONMEM program
- Number of significant digits ≥ 3; if the number of significant digits is <3, reasons for acceptance of the NONMEM run are given.
- Estimates of THETA not close to boundary

Base model evaluation was mainly focus on the selection of residual error model (additive error model, proportional error model, and combined error model) and the inter-individual random effect (normally distributed or log-normal distributed).

Full model was developed to identify possible covariates. The full model was selected by using forward inclusion and backward elimination with the following steps:

- Graphical evaluation of the correlation between individual parameter estimates for k_e and V/f from the base model and potential covariates.
- After the graphical evaluation of the parameter-covariate relationships, each covariate was tested on each of the model parameters k_e and V/f by adding 1 covariate at a time (and removing it) and recording the resulting NONMEM OBF.
- Each of the potential covariates, starting with the "most significant" covariate (=largest OBF difference), was added to the model ("forward inclusion"). If the addition of a potential covariate caused a >3.841-point-decrease of the OBF ($p<0.05$, likelihood ratio test), the covariate was considered as a potentially significant covariate and was added to the model; otherwise, the covariate was dropped from the model. This resulted in building of the "full" model by including all potentially significant covariates.
- In the next step, each potentially significant covariate was removed from the full model individually to determine if a model with fewer parameters would describe the data ("backward stepwise elimination"). If the removal of a potentially significant covariate caused an increase in OBF of at least 7.88 points ($p<0.005$, likelihood ratio test), the covariate was retained in the "final" model; otherwise, the covariate was dropped from the model. In the last step, the residual error model was tested again.

5.3.1.1.5 RESULTS:

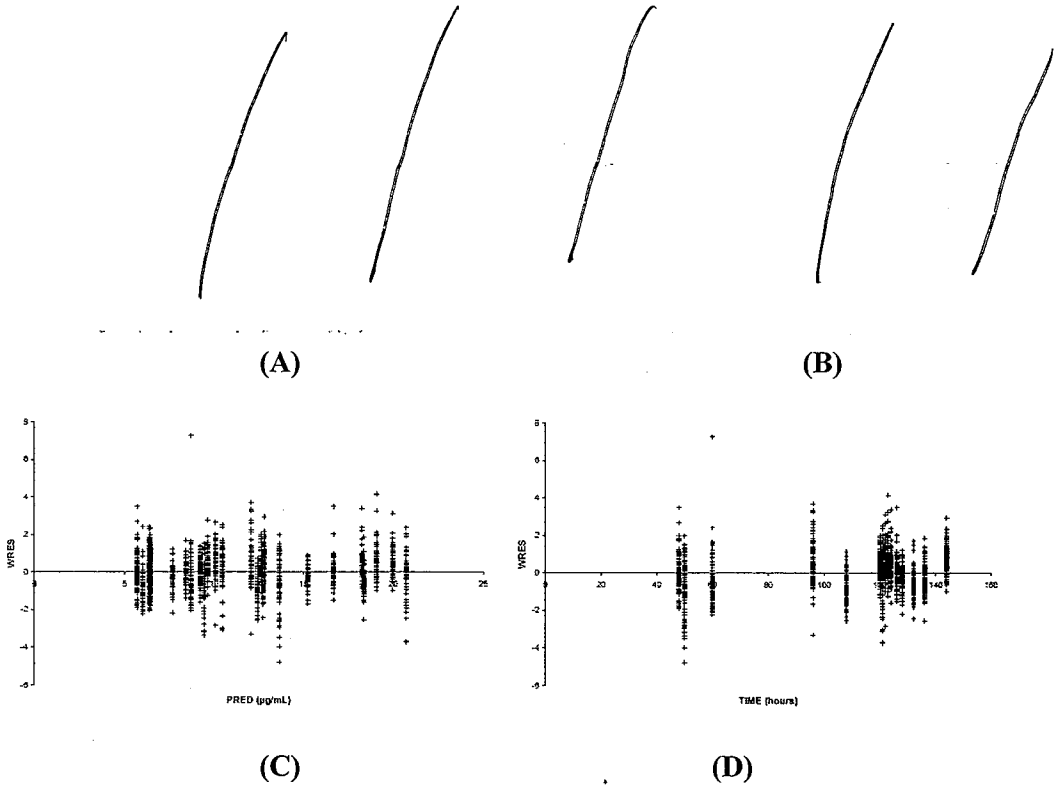
The structure model for the final base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ke, and V/f. Ka was fixed to 4.00 1/hr. The residual was described as the proportional error model. The model parameter estimates were summarized in Table 2 and the major goodness-of-fit plots were shown in Figure 5 .

Table 2 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial SP640

Parameters	Estimates	Relative Standard Error [%]
Ka [1/hr]	4	not applicable

Ke [1/hr]	0.045	1.74
V/f [L]	43.8	2.05
IIV on Ka [%]	Fixed	not applicable
IIV on Ke [%]	15.1	15.9
IIV on V/f [%]	16.8	13
Proportional Residual Error [%]	7.83%	7.52

Figure 5 Goodness-of-fit Plots for Lacosamide Base Population PK Model Derived from Trial SP640



Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effect and parameter estimates were summarized in Table 3. Goodness-of-fit plots were shown in Figure 6.