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

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

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

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

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

**Table 2: Summary of Urinary PK**

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

a 8-12 h after dosing N = 11

b 36-48 h after dosing N = 11

*Data source: Section 13.2, Table 10.2.7*

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

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

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

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

*4.2.2.2 Dose Proportionality Studies—Multiple Doses*

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

---

**Study Type:** Multiple dose study.

b(4)

**Clinical Investigator:** [redacted]

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

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

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

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

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

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

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

Analytical Methodology: Same as Study SP835

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

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

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

Descriptive statistics for PK parameters of shown Table 1.

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

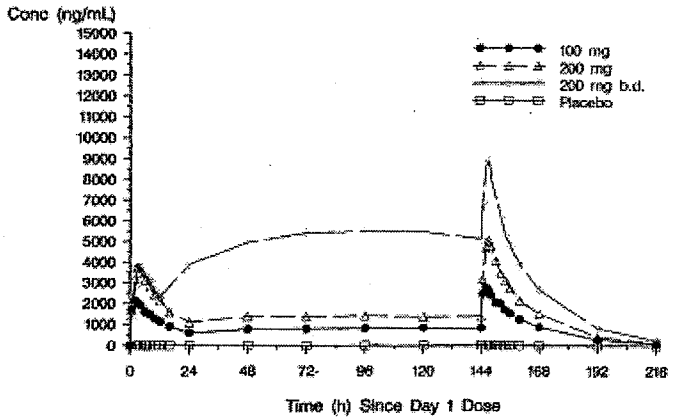
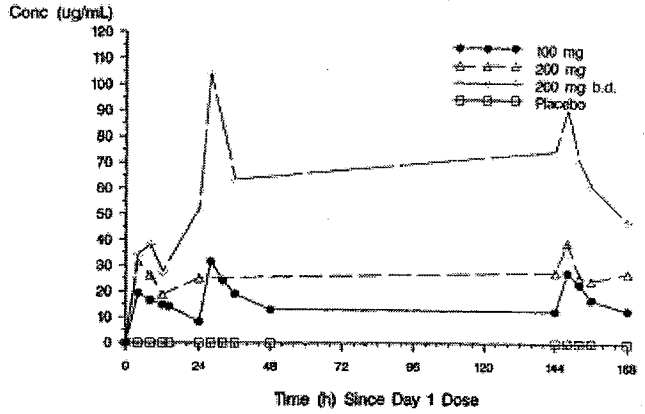


**Figure 2.** Mean Urinary Concentrations of SPM 927 After Oral Administration of SPM mg to Healthy Volunteers.






## Table 1: Summary of PK Parameters

| Dose | 100 mg od | | 200 mg od | | 200 mg b.i.d. | |
|---|---|---|---|---|---|---|
| $C_{max}$ | Day 1 | Day 7 | Day 1 | Day 7 | Day 1 | Day 7 |
| Mean | 2232.1 | 2955.3 | 3855.4 | 5167.6 | 4052.3 | 8902.6 |
| SD | 328.6 | 476.9 | 270.5 | 648.4 | 596.3 | 1426.7 |
| Median | 2151.8 | 2834.8 | 3961.5 | 5247.4 | 4205.9 | 8284.9 |
| CV% | 14.7 | 16.2 | 7.0 | 12.5 | 14.7 | 16.0 |
| Minimum | 1908.9 | 2426.1 | 3436.0 | 4022.9 | 3435.6 | 7571.7 |
| Maximum | 2701.1 | 3764.4 | 4144.9 | 5858.5 | 4857.4 | 11149.4 |
| N | 6 | 6 | 6 | 6 | 5 | 5 |
| $T_{max}$ (h) | | | | | | |
| Mean | 1.750 | 1.333 | 3.167 | 2.833 | 3.200 | 2.400 |
| SD | 0.880 | 0.753 | 1.472 | 0.753 | 0.837 | 0.548 |
| Median | 2.000 | 1.500 | 3.000 | 3.000 | 3.000 | 2.000 |
| CV% | 50.305 | 56.458 | 46.483 | 26.568 | 26.146 | 22.822 |
| Minimum | 0.500 | 0.500 | 2.000 | 2.000 | 2.000 | 2.000 |
| Maximum | 3.000 | 2.000 | 6.000 | 6.000 | 4.000 | 3.000 |
| N | 6 | 6 | 6 | 6 | 5 | 5 |
| $AUC_{0\text{-}12}$ | | | | | | |
| Mean | 18963.1 | 25244.1 | 33048.3 | 45466.7 | 34233.1 | 81369.3 |
| SD | 2169.2 | 3526.2 | 2528.7 | 5933.2 | 4439.7 | 11250.4 |
| Median | 19047.0 | 25465.4 | 33759.8 | 47388.8 | 34963.8 | 75023.4 |
| CV% | 11.4 | 14.0 | 7.7 | 13.0 | 13.0 | 13.8 |
| Minimum | 16476.7 | 21130.5 | 28768.2 | 34834.4 | 28767.5 | 72158.6 |
| Maximum | 21300.0 | 30833.0 | 35455.4 | 51569.0 | 40384.5 | 98587.2 |
| N | 6 | 6 | 6 | 6 | 5 | 5 |
| $AUC_{0\text{-}72}$ (h·ng/mL) | | | | | | |
| Mean | -- | 57220.7 | -- | 98610.0 | -- | 178352.1 |
| SD | -- | 9583.5 | -- | 23554.9 | -- | 20453.9 |
| Median | -- | 57329.7 | -- | 100247.5 | -- | 180537.4 |
| CV% | -- | 16.7 | -- | 23.9 | -- | 11.5 |
| Minimum | -- | 46363.7 | -- | 61457.4 | -- | 156874.8 |
| Maximum | -- | 71399.0 | -- | 123825.7 | -- | 204049.5 |
| N | -- | 6 | -- | 6 | -- | 5 |
| $AUC_{0\text{-}\infty}$ | | | | | | |
| Mean | -- | 59129.0 | -- | 101068.7 | -- | 183309.2 |
| SD | -- | 10343.8 | -- | 24998.8 | -- | 21433.9 |
| Median | -- | 58884.9 | -- | 102726.2 | -- | 188436.4 |
| CV% | -- | 17.5 | -- | 24.7 | -- | 11.7 |
| Minimum | -- | 47224.5 | -- | 61902.9 | -- | 159509.5 |
| Maximum | -- | 73624.6 | -- | 127009.3 | -- | 209133.8 |
| N | -- | 6 | -- | 6 | -- | 5 |
| $\lambda$ Values (/h) | | | | | | |
| Mean | -- | 0.048 | -- | 0.054 | -- | 0.050 |
| SD | -- | 0.005 | -- | 0.008 | -- | 0.004 |
| Median | -- | 0.049 | -- | 0.051 | -- | 0.050 |
| CV% | -- | 10.6 | -- | 14.7 | -- | 8.9 |
| Minimum | -- | 0.040 | -- | 0.045 | -- | 0.044 |
| Maximum | -- | 0.055 | -- | 0.068 | -- | 0.056 |
| N | -- | 6 | -- | 6 | -- | 5 |
| $t_{1/2}$ (h) | | | | | | |
| Mean | -- | 14.47 | -- | 13.02 | -- | 13.91 |
| SD | -- | 1.67 | -- | 1.80 | -- | 1.23 |
| Median | -- | 14.20 | -- | 13.50 | -- | 13.81 |
| CV% | -- | 11.54 | -- | 13.80 | -- | 8.99 |
| Minimum | -- | 12.70 | -- | 10.26 | -- | 12.23 |
| Maximum | -- | 17.48 | -- | 15.47 | -- | 15.80 |
| N | -- | 6 | -- | 6 | -- | 5 |

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

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

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

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

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

---

**Study Type:** Multiple dose study.

**Clinical Investigator:** [redacted] b(4)

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

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

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

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

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

Analytical Methodology : Same as Study 587

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

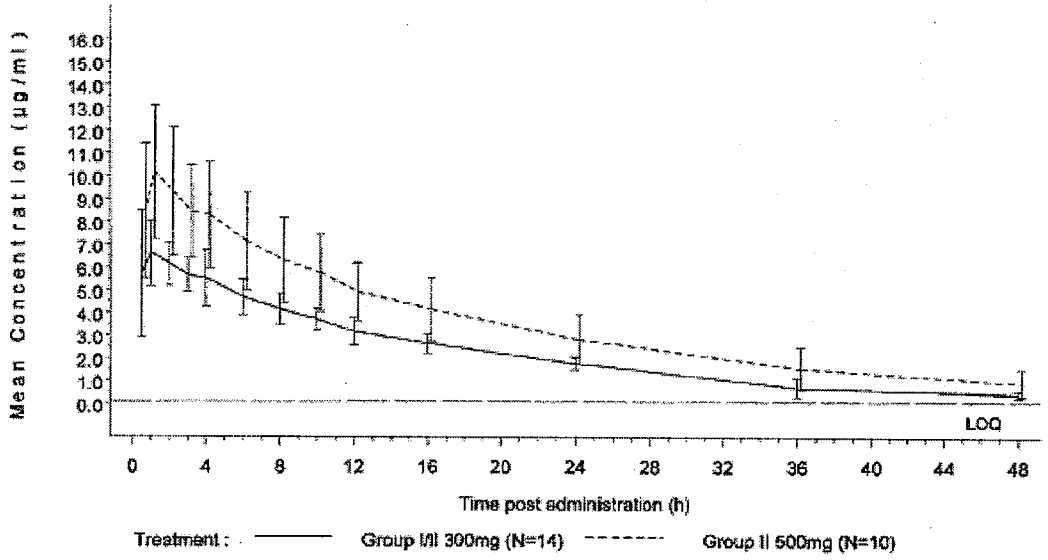
**Results:**

Study Population: 33 male Caucasian subjects were enrolled. Fourteen and Twelve subjects completed the single dose and multiple dose of 300 mg SPM respectively while 10 and 4 completed the single and multiple dose of 500 mg SPM respectively.

Pharmacokinetics: PK parameters were derived from non-compartmental analysis. Trough concentrations of SPM indicate that with a twice-daily dosing regimen with 200 mg LCM, steady state was reached after 72 hours.

The following figure shows mean plasma concentrations of LCM over 48 hours after administration of a single dose of 300 mg and 500 mg LCM.

**Figure 1. Mean plasma concentration-time curve of LCM (mean and standard deviation) after administration of a single dose of 300 mg and 500 mg LCM.**




Descriptive statistics for PK parameters of shown Tables 1 to 4.

**Table 1: Single Dose PK (Mean±SD or Median (range))**

| | | 300 mg (N=14, group I/II) | 500 mg (N=10, group II) |
|---|---|---|---|
| $AUC_{0\rightarrow t\text{-last}}$ | [µg*h/ml] | 104.9 ± 13.8 | 168.7 ± 52.9 |
| $AUC_{0\rightarrow\infty}$ | [µg*h/ml] | 111.9 ± 16.0 | 190.1 ± 65.4 |
| $C_{max}$ | [µg/ml] | 7.6 ± 2.0 | 10.4 ± 3.0 |
| $t_{max}$ * | [h] | 1.0 (0.5-4.0) | 1.0 (0.5-2.0) |
| $t_{1/2}$ * | [h] | 11.6 (8.1-17.7) | 13.3 (8.6-19.1) |
| $Cl_{tot}/F$ | [l/h] | 2.7 ± 0.4 | 3.1 ± 1.6 |
| $V_z/F$ | [l] | 45.1 ± 9.4 | 57.1 ± 22.7 |
| MRT* | [h] | 17.1 (12.0-24.4) | 19.4 (12.5-28.0) |

*Data source: Section 13.1, Table 10.2.3.1*

**Table 2: Multiple Dose PK (Mean±SD or Median (range))**

| | 300 mg (N=12, Group I) | | 400 mg (N=7, Group II) | | 500 mg (N=4, Group II) | |
|---|---|---|---|---|---|---|
| | Day 15 night | Day 16 day | Day 15 night | Day 16 day | Day 15 night | Day 16 Day |
| $AUC_{12\rightarrow24h}$ [µg*h/ml] | 119.4 ± 18.3 | | 163.3 ± 40.1 | | 115.6 ± 60.6 | |
| $AUC_{0\rightarrow12h}$ [µg*h/ml] | | 126.0 ±17.4 | | 171.1 ± 32.7 | | 118.0 ± 75.6 |
| $C_{max}$ [µg/ml] | 12.6 ± 2.2 | 14.5 ±1.7 | 16.1 ± 3.4 | 19.2 ± 3.7 | 12.8 ± 6.3 | 13.5 ± 8.4 |
| $C_{min}$ [µg/ml] | 7.7 ± 1.4 | 7.4 ±1.2 | 11.1 ± 3.4 | 10.4 ± 2.8 | 6.9 ± 3.8 | 6.2 ± 4.2 |
| $t_{max}$* [h] | 3 (1-6) | 1.0 (1-2) | 4.0 (2-6) | 1.0 (1-4) | 2.0 (1-6) | 1.5 (0-2) |
| $t_{1/2}$* [h] | | 12.4 (8.1-17.4) | | 12.2 (7.8-17.6) | | 8.7 (7.6-15.2) |
| $Cl_{tot}/F$ [l/h] | 2.6 ±0.4 | 2.4 ±0.4 | 2.6 ±0.7 | 2.4 ±0.5 | 4.0* (2.8-15.5) | 3.8* (2.5-33.6) |
| MRT* [h] | 26.1 (18.1-39.3)[1] | 18.0 (12.9-24.5) | 38.6 (21.4-55.9)[2] | 17.3 (13.4-25.5) | 15.4 (14.6-16.6)[3] | 13.1 (12.1-20.4) |

*Data source: Section 13.1, Tables 10.2.3.3 and 10.2.3.4*
[1]N=6; [2]N=2; [3]N=3

**Table 3: Single Dose Urinary PK of SPM 927 (Mean±SD)**

| | | 300 mg | | 500 mg |
|---|---|---|---|---|
| Time | N | Amount excreted [mg] | N | Amount excreted [mg] |
| 0 h | 13 | 2.5 ± 0.0 | 10 | 2.5 ± 0.0 |
| 0 – 4 h | 13 | 29.3 ±15.8 | 10 | 60.3 ± 70.0 |
| 4 – 8 h | 13 | 47.2 ±18.9 | 10 | 59.4 ± 20.6 |
| 8 – 12 h | 13 | 39.4 ±15.8 | 10 | 54.2 ± 25.5 |
| 12 – 24 h | 13 | 31.0 ± 9.0 | 10 | 48.7 ± 31.2 |
| 24 – 36 h | 13 | 12.3 ± 3.9 | 10 | 23.7 ± 18.1 |
| 36 – 48 h | 11 | 6.7 ± 4.1 | 9 | 16.6 ± 12.3 |
| Total | (13) | 167.3 ± 53.4 | (10) | 263.7 ± 132.7 |
| | N | Renal clearance [l/h] | N | Renal clearance [l/h] |
| | 13 | 1.5 ± 0.4 | 10 | 1.4 ± 0.4 |

*N=number of subjects*

*Data source: Section 13.1, Table 10.2.10.1*

**Table 4: Multiple Dose Urinary PK of SPM 927 (Mean±SD)**

| | 300 mg (N=12, group I) | 500 mg (N=4, group II) | 400 mg (N=7, group II) |
|---|---|---|---|
| Time | | Amount excreted [mg] | |
| 0 – 4 h | 56.7 ± 23.3 | 51.5 ± 32.1 | 103.3 ± 28.2 |
| 4 – 8 h | 88.7 ± 30.1 | 64.3 ± 45.5 | 124.5 ± 27.6 |
| 8 – 12 h | 92.3 ± 77.6 | 74.0 ± 74.2 | 125.7 ± 58.2 |
| Total (0-12h) | 237.7 ± 88.5 | 189.8 ± 145.3 | 353.6 ± 96.1 |
| 12 – 24 h | 72.2 ± 26.1 | 48.6 ± 48.1 | 101.9 ± 58.8 |
| 24 – 36 h | 29.0 ± 16.3 | 17.1 ± 16.0 | 55.6 ± 43.4 |
| 36 – 48 h | 19.4 ± 8.6 | 6.4 ± 5.8 | 22.4 ± 13.3 |
| | | Renal clearance [l/h] | |
| | 1.8 ± 0.6 | 1.7 ± 0.4 | 2.1 ± 0.3 |

*Data source: Section 13.1, Tables 10.2.10.3*

The PK characteristics after single-dose administration of 300 and 500mg LCM in this trial were comparable to those observed in SP587 (single-dose administration of 400, 600, and 800mg LCM).

No relevant differences were apparent for tmax, t1/2, and CLrenal between single- and multiple-dose (over 13 days) administration of LCM.

Trough concentrations indicate that steady state was reached within 3 days.

**Conclusions**: The PK characteristics of LCM in this trial were consistent with those obtained in previous trials. AUC and Cmax increased proportionally with the administered dose. The PK characteristics did not change during multiple dosing, ie, multiple-dose pharmacokinetics could be predicted from single dose data. The analysis of $AUC_{(0\text{-}tz)}$, $AUC_{(0\text{-}\infty)}$, and $C_{max}$ of LCM showed dose-proportional increases for these parameters.

*4.2.3 Special Population Studies*

*4.2.3.1 Renal Impairment— Study SP641: Open, non-randomized, sequential group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 in male and female subjects with renal impairment including subjects requiring dialysis compared with male and female healthy subjects following single-dose administration*

---

| | |
|---|---|
| **Study Period:** | June 4, 2004 to November 22, 2004 |
| **Sample Analysis Periods:** | November 22, 2004 to February 18, 2005 (plasma)<br>December 13, 2005 to December 16, 2005 (urine) |
| **Analytical Site:** | SCHWARZ BIOSCIENCES GmbH, Department of Bioanalytics, Alfred-Nobel-Straße 10, 40789 Monheim am Rhein, Germany |

| | | |
|---|---|---|
| **Name of company:** SCHWARZ BIOSCIENCES GmbH | **Individual study table referring to part of the dossier** NA | *(For National Authority Use Only)* |
| **Name of Finished Product:** Not applicable | **Volume:** Not applicable | |
| **Name of Active Ingredient:** Lacosamide | **Page:** Not applicable | |

**Title of trial:** Open, non-randomized, sequential group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 in male and female subjects with renal impairment including subjects requiring dialysis compared with male and female healthy subjects following single-dose administration

**Investigators:** [redacted] b(4)

**Trial sites:** 2 sites in Germany

**Publication (reference):** None

| | |
|---|---|
| **Studied period (years):** - | **Phase of development:** Phase 1 |
| **First subject enrolled:** 04 Jun 2004 | |
| **Last subject completed:** 22 Nov 2004 | |

**Objectives:** Primary objective of Part 1 of the trial was to evaluate the pharmacokinetics of lacosamide in subjects with mild to severe renal impairment, stratified according to their creatinine clearance approximately 2 to 7 days prior to dosing, and healthy subjects (individually matched to subjects from Group 4 for age, body mass index [BMI], and gender) following single-dose administration of 100mg lacosamide. A comparison of pharmacokinetic (PK) parameters was performed to assess whether renal impairment is associated with changes in pharmacokinetics.

Primary objective of Part 2 of the trial was to evaluate the pharmacokinetics of lacosamide in subjects with endstage renal disease requiring dialysis under dialysis and non-dialysis conditions following single-dose administration of 100mg lacosamide.

As secondary objectives further pharmacokinetics of the main metabolite of lacosamide and the safety and tolerability of the treatment were evaluated.

**Methodology:** This was an open-label, non-randomized, non-controlled, sequential group comparison trial in 2 parts in subjects with renal impairment and in healthy subjects.

Part 1 was a sequential group comparison trial. Male and female subjects (healthy and with renal impairment) were assigned to 1 of 4 groups according to their creatinine clearances ($CL_{Cr}$) (Groups 1 to 4). All subjects received a single-dose of 100mg lacosamide.

Part 2 was a trial with 2 treatments in a fixed order (A-B). Male and female subjects with endstage renal disease requiring dialysis (Group 5) received the following treatments:

Treatment A: single dose of 100mg lacosamide on dialysis-free day (1 day before dialysis)

Treatment B: single dose of 100mg lacosamide 2.5 hours before the start of hemodialysis (duration of hemodialysis: 4 hours)

| |
|---|
| **Number of subjects (planned and analyzed)**: Thirty-two subjects were enrolled in Part 1 as planned (in 4 groups of 8 subjects). Eight subjects were enrolled in Part 2 as planned (Group 5). All subjects completed the trial and were valid for PK and safety analysis. |
| **Diagnosis and main criteria for inclusion**: Subjects were healthy or had impaired renal function (mild, moderate, severe, or endstage renal impairment requiring dialysis) and were assigned to groups according to their $CL_{Cr}$ values at the Eligibility Assessment. Healthy subjects (Group 1) were individually matched to subjects from Group 4 for age, BMI, and gender. |
| **Test product, dose and mode of administration, batch number**: Single oral dose of lacosamide 100mg film-coated tablet; drug product batch number: 228920; pack batch number: 20030204 |
| **Duration of treatment**: Single dose |
| **Reference therapy, dose and mode of administration, batch number**: None |
| **Criteria for evaluation**:<br><br>Pharmacokinetics: Primary PK parameters were:<br><br>Part 1: $AUC_{(0-tz)}$, $AUC_{(0-tz)norm}$, $C_{max}$, and $C_{max,norm}$ of lacosamide<br><br>Part 2: $AUC_{(0-tz)}$, $AUC_{(0-tz)norm}$, $C_{max}$, $C_{max,norm}$ of lacosamide<br><br>Secondary PK parameters were:<br><br>Part 1: C(t) and $t_{max}$ of lacosamide, CL/f, $CL_R$, and $t_{1/2}$ of lacosamide, $AUC_{(0-tz)}$, $AUC_{(0-tz)norm}$, $C_{max}$, $C_{max,norm}$, $CL_R$, and $t_{1/2}$ of the main metabolite (SPM 12809), $A_{e(0-t)}$ and $t_{1/2,ur}$ of lacosamide and SPM 12809<br><br>Part 2: C(t) and $t_{max}$ of lacosamide, CL/f and $t_{1/2}$ of lacosamide, $AUC_{(0-tz)}$, $AUC_{(0-tz)norm}$, $C_{max}$, $C_{max,norm}$, and $t_{1/2}$ of SPM 12809, concentration of lacosamide and SPM 12809 in dialysis inlet and outlet line at t=6 hours (3.5 hours after start of dialysis) to calculate E (extraction rate) during dialysis, concentration of lacosamide and SPM 12809 in the dialysis fluid at t=4 hours (1.5 hours after start of dialysis) and at the end of dialysis to calculate $CL_{dial}$<br><br>Safety: Subjective tolerability, adverse events (AEs), determination of changes in laboratory parameters, and influence on vital sign parameters (pulse rate, blood pressure) and electrocardiogram (ECG) |

**Rationale for the study:** Lacosamide is eliminated primarily via renal excretory mechanisms. Data from previous studies show that about 40% of the administered dose were excreted renally as unchanged lacosamide and another 30% were excreted as the main metabolite, SPM 12809. In addition, a 20% polar fraction was excreted in urine. Impaired renal function may alter the pharmacokinetics of drugs with such mechanisms of excretion and the dosage regimen may need to be adjusted in patients with renal impairment. Pharmacokinetic characterization in subjects with renal impairment would provide rational recommendations for dosing in renal impairment patients.

**Dose selection:** In this trial a dose of 100mg, which represents the lowest therapeutic dose, was chosen for safety considerations. The proposed therapeutic doses are 50-— mg twice daily. The classification of renal function and stratification were based the FDA 1998 renal guidance. b(4)

Group 1: $CL_{Cr} \geq 80mL/min$ (healthy subjects)

Group 2: $80mL/min > CL_{Cr} \geq 50mL/min$ (subjects with mild renal impairment)

Group 3: $50mL/min > CL_{Cr} \geq 30mL/min$ (subjects with moderate renal impairment)

Group 4: $CL_{Cr} < 30mL/min$ (subjects with severe renal impairment, not on dialysis between 2 weeks before EA and end of the trial)

In Group 4 the whole range of $CL_{Cr}$ values had to be covered, ie, 4 subjects with $CL_{Cr}$ values of 20-30mL/min and 4 subjects with $CL_{Cr}$ <20mL/min were enrolled.

Subjects of Group 4 were included only after uneventful treatment of at least 6 subjects with mild (Group 2) or moderate (Group 3) renal dysfunction.

Healthy subjects (Group 1) were individually matched by age, BMI, and gender to subjects of Group 4.

Group 5: Subjects with endstage renal disease ($CL_{Cr}$<15mL/min, determined 2 to 7 days before first dosing) treated with extracorporal hemodialysis for at least 4 months

Subjects for Part 2 were only enrolled at Site 1.

The materials used for dialysis in Part 2 (eg, filters and tubes) were not examined for a possible interference with the analytes because this was not necessary in the opinion of the responsible analyst. In addition, no discrepancy was found between the results for the extraction rate, the amount excreted in the dialysis fluid, and the reduction of $AUC_{(0-tz)}$ for lacosamide and SPM 12809.

For the high-flux hemodialysis in Part 2 of the trial, a —— dialysator type —— with a blood flow rate of 300mL/min and a dialysate flow rate of 500mL/min was used. Samples for PK evaluation were drawn from the dialysis inlet and dialysis outlet line 4 hours after the start of dialysis and from the dialysis fluid 4 and 6.5 hours after the start of dialysis. b(4

**Subjects:** Eight subjects were enrolled in each of the 5 groups. All subjects were valid for safety and PK analyses (Table 1). All subjects were White. Subjects in Group 1 were individually matched to subjects in Group 4.

**Table 1. Demographic Summary.**

**Demographic characteristics of Groups 1 to 5 - SS**

| Variable | Statistic | Group 1 (N=8) | Group 2 (N=8) | Group 3 (N=8) | Group 4 (N=8) | Group 5 (N=8) |
|---|---|---|---|---|---|---|
| Gender<br>- Male<br>- Female | <br>n<br>n | <br>4<br>4 | <br>8<br>0 | <br>2<br>6 | <br>4<br>4 | <br>7<br>1 |
| Age (years) | Mean±SD (range) | 56.4±8.2 (44-66) | 50.9±12.8 (25-63) | 47.6±10.2 (37-65) | 57.9±10.7 (38-68) | 43.1±8.8 (27-54) |
| Body height (cm) | Mean±SD (range) | 171.8±10.4 (155-189) | 175.1±5.5 (170-187) | 168.9±7.7 (160-181) | 169.0±8.5 (157-182) | 172.0±8.7 (160-184) |
| Body weight (kg) | Mean±SD (range) | 76.2±14.8 (59-101) | 83.0±10.2 (71-99) | 71.5±9.5 (57-86) | 70.5±14.0 (60-104) | 71.8±13.7 (54-101) |
| BMI ($kg/m^2$) | Mean±SD (range) | 25.6±2.7 (23-32) | 27.1±3.1 (23-33) | 25.1±3.2 (20-32) | 24.6±3.6 (21-33) | 24.3±4.1 (21-33) |

BMI=body mass index; SD=standard deviation; SS=Safety Set

Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment; Group 5=subjects with endstage renal disease, requiring hemodialysis

**Table 2.**

**Creatinine clearance (mL/min) in Groups 1 to 5 at Eligibility Assessment - SS**

| Variable | Statistic | Group 1 (N=8) | Group 2 (N=8) | Group 3 (N=8) | Group 4 (N=8) | Group 5 (N=8) |
|---|---|---|---|---|---|---|
| Creatinine clearance | Range | 82.30-142.10 | 52.80-77.10 | 30.10-47.80 | 10.40-28.80 | 8.00-17.80 [a] |

SS=Safety Set

Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment; Group 5=subjects with endstage renal disease, requiring hemodialysis

[a] Without Subject 80505 who had a creatinine clearance of 17.80mL/min at EA, the range of values in Group 5 was 8.00-14.90mL/min.

**Sample Collection:**

*Plasma samples:*

For quantification of lacosamide and its metabolite, 17 venous blood samples of 6 mL were collected from predose to 96 hours post dose in Part 1. 30 samples of 4mL were collected in Part 2 (15 samples per treatment) (see Table 3 below). Samples for PK evaluation were drawn from the dialysis inlet and dialysis outlet line 4 hours after the start of dialysis and from the dialysis fluid 4 and 6.5 hours after the start of dialysis (Table 3). Two samples of about 1.5mL were collected for each time point. The dialysis fluid was collected in a container and weighed after 4

and 6.5 hours to determine the collected volume. The total volume collected after 4 and 6.5 hours and the concentrations of lacosamide and SPM 12809 in the dialysis fluid were used to calculate the amounts excreted by dialysis at these timepoints.

**Table 3.**

TABULAR SCHEDULE FOR SAMPLING FOR PHARMACOKINETICS (PART 2)

| Day (d) | Time schedule (hh:mm) | Time schedule (min postdose) | Treatment A (without hemodialysis) | Treatment B (with dialysis) | Dialysis |
|---|---|---|---|---|---|
| 1 | 00:00 | 0 (predose) | X | X (predose) | |
| | 00:30 | 30 | X | X | |
| | 01:00 | 60 | X | X | |
| | 01:30 | 90 | X | X | |
| | 02:00 | 120 | X | X | |
| | 02:30 | 150 | X | X (prior to start of dialysis) | ↓ |
| | 02:45 | 165 | | X | |
| | 03:00 | 180 | X | X | |
| | 03:30 | 210 | | X | |
| | 04:00 | 240 | X | X[a] | |
| | 06:00 | 360 | X | X | |
| | 06:30 | 390 | | X[b] | |
| | 06:50 | 410 | | X | |
| | 08:00 | 480 | X | X | |
| | 12:00 | 720 | X | X | |
| 2 | 24:00 | 1440 | X | X | |

oint, additional samples were drawn from the dialysis inlet and dialysis outlet line as well as from the dialysis fluid.

oint, an additional sample was drawn from the dialysis fluid.

*Urine samples:*

Urine was collected for the determination of renal excretion of lacosamide and SPM 12809 during the following collection period in Part 1 of the trial:

- Predose (blank) (Day 1)
- 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hours postdose

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method using Positive Electrospray Ionization (ESI) and Selected Reaction Monitoring (SRM) in plasma (Validation Report No.ba583-03) and urine (Validation Report No. 585-02). The LOQ for LCM in plasma was 0.01 µg/mL and in urine was 0.2 µg/mL. The LOQ for SPM 12809 in plasma was 0.01 µg/mL and in urine was 0.2 µg/mL. See tables below for summary of analytical assay data.

**Parameters of the assayed standard concentrations and the calibration curves**

| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of correlation 'r' | Precision of slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.2 - 6.3 | 96.4 - 107.4 | 0.9999 | 8.0% |
| SPM 12809 | 0.7 - 6.5 | 97.6 - 102.6 | 0.9997 | 16.5% |

**Parameters of the assayed standard concentrations and the calibration curves**

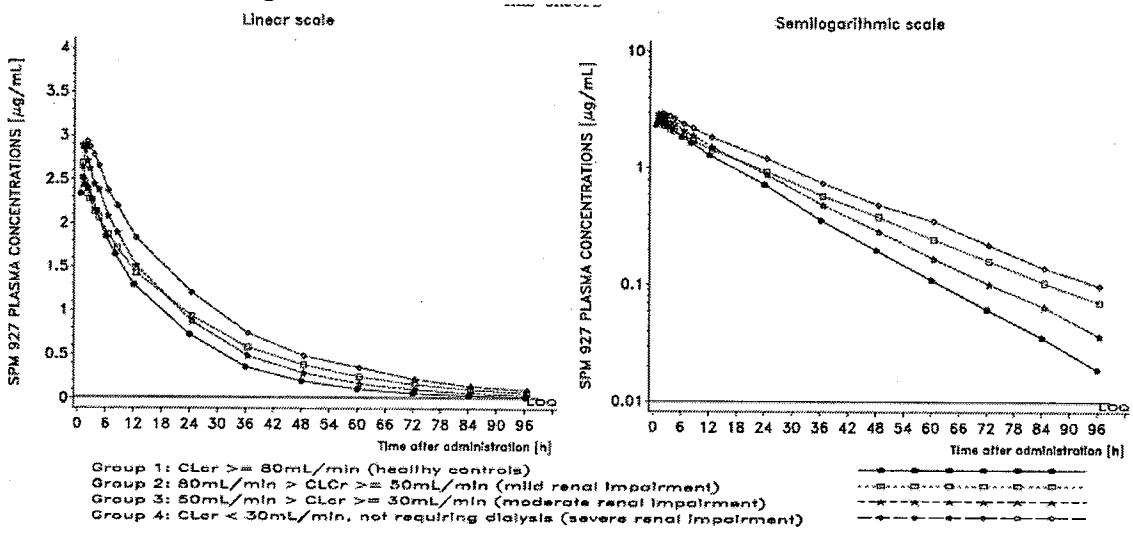
| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of correlation 'r' | Precision of slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.8 - 3.7 | 88.3 - 108.3 | 0.99714 | 0.5% |
| SPM 12809 | 0.3 - 4.3 | 93.4 - 103.0 | 0.99928 | 1.1% |

**Pharmacokinetic Results:**

***Part 1: Normal to Severe Renal Impairment***

*Lacosamide:*

Plasma concentration-time profiles for lacosamide in subjects with different degree of remal function are shown in Figure 1.




Note: Values below LOQ (=0.01µg/mL) were replaced by zero in calculations of mean and SD if at least 2/3 of the data were above LOQ.

**Figure 1. Mean plasma concentrations of lacosamide after single oral administration of 100mg lacosamide in healthy subjects and subjects with mild to severe renal impairment.**





b(4)

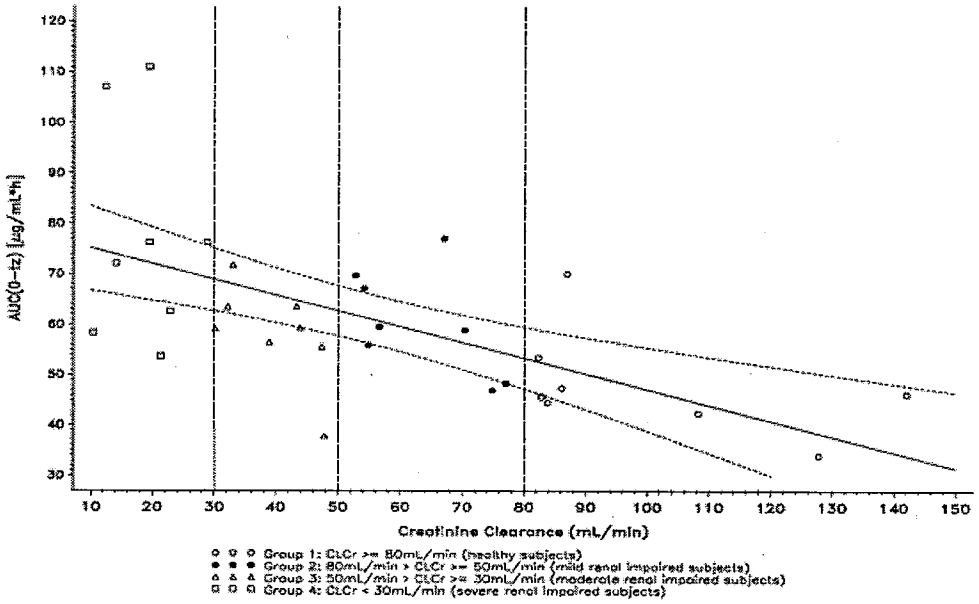
**Table 4. Pharmacokinetic parameters of lacosamide in healthy subjects compared with subjects with mild to severe renal impairment.**

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

CV=coefficient of variation; PKS=Pharmacokinetic Set
Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment
[a] Median (range)
[b] Arithmetic mean ± standard deviation
[c] Summary statistics calculated for N=7 subjects only: no urine PK parameters were calculated for Subject 80306 due to incomplete urine collection.

The plot of relationship between individual values of $AUC_{(0-tz)}$ of lacosamide and the $CL_{Cr}$ in healthy subjects (Group 1) and subjects with mild, moderate, and severe renal impairment (Groups 2-4) is shown in Figure 2 and Figure 3, respectively.

APPEARS THIS WAY
ON ORIGINAL




$CL_{Cr}$=creatinine clearance; PKS=Pharmacokinetic Set

Note: The solid line represents the regression line and the dashed line represents the 95% confidence interval.

**Figure 2. Plot of relationship of $AUC_{(0\text{-}tz)}$ of lacosamide and $CL_{Cr}$ in healthy subjects and subjects with mild to severe renal impairment.**

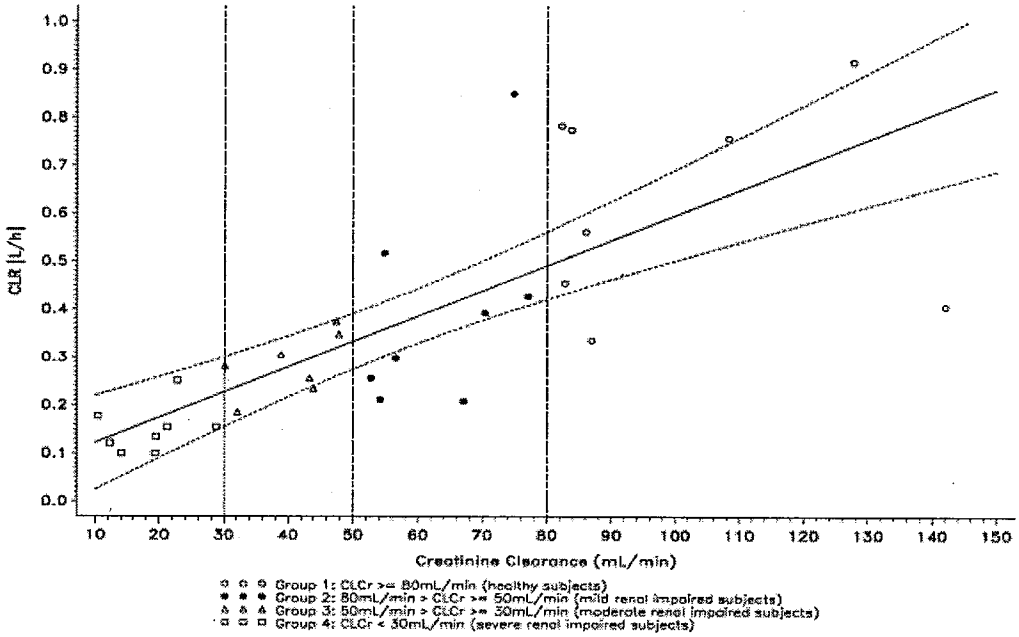



**Figure 3. Plot of relationship of $CL_R$ of lacosamide and $CL_{Cr}$ in healthy subjects and subjects with mild to severe renal impairment.**

**Table 5.**

**ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for primary PK parameters of lacosamide - PKS**

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

ANOVA=analysis of variance; PK=pharmacokinetic; PKS=Pharmacokinetic Set

Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment

Data showed that the systemic exposure of lacosamide (AUC) increased with increasing degree of renal impairment (Tables 4 and 5 and Figure 2). Mean AUC increased 27%, 23%, and 59% in subjects with mild, moderate, and severe renal impairment compared with healthy subjects, respectively (Table 5). AUC values were more variable for patients with severe renal impairment, AUC in some patients were 2-fold higher than AUC in healthy subjects. Overall, renal clearance of lacosamide decreased with increasing degree of renal impairment (Table 4 and Figure 3).

For $C_{max}$, only a slight difference was observed. The terminal half-life of lacosamide in plasma ($t_{1/2}$) was prolonged in subjects with severe renal impairment (approximately 18 hours) in comparison with healthy subjects (approximately 13 hours) (Table 4).

*SPM 12809:*

Mean AUC(0-tz) and Cmax of SPM 12809 increased with increasing degree of renal impairment. The increases were more profound than lacosamide. AUC increased 4-fold in patients with severe renal impairment compared to normal renal function subjects (Tables 6 and 7). The tmax (median and range) and mean t1/2 of SPM 12809 were prolonged with increasing degree of renal impairment (Figure 4).

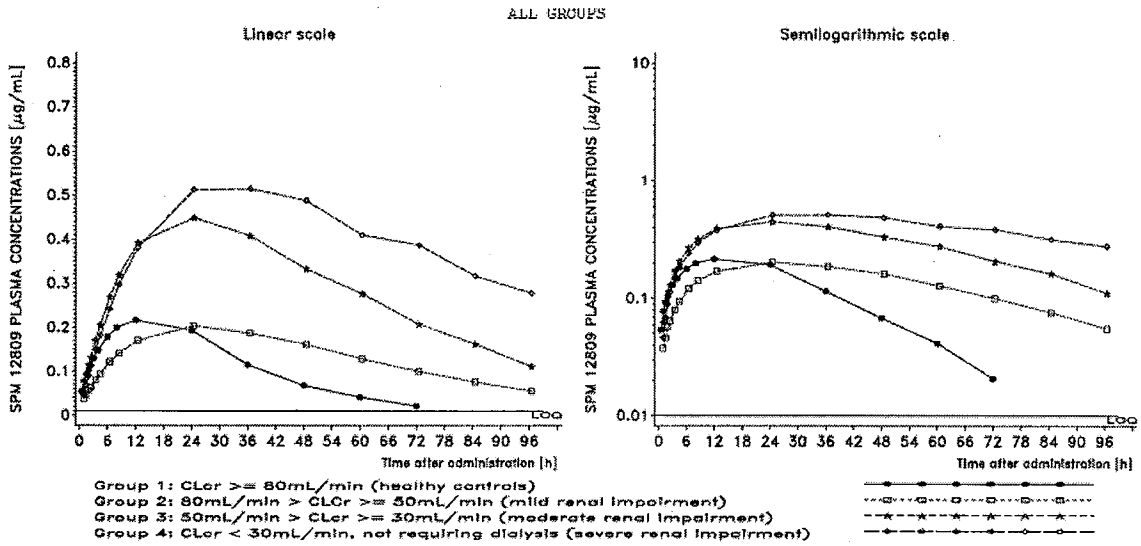



**Figure 4. Mean plasma concentrations of SPM 12809 after single oral administration of 100mg lacosamide in healthy subjects and subjects with mild to severe renal impairment.**

**Table 6. Pharmacokinetic parameters of SPM 12809 in healthy subjects compared with subjects with mild to severe renal impairment.**

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

CV=coefficient of variation;
Group 1=healthy subjects; Group 2=subjects with mild renal impairment; Group 3=subjects with moderate renal impairment; Group 4=subjects with severe renal impairment
[a] Median (range)
[b] Limitations for the calculation of CL/f and CLR in this trial are described in Section 4.1.1.

c Summary statistics calculated for N=7 subjects only. Group 3: PK parameters $A_{e(0-48)}$ and $CL_R$ were not calculated for Subject 80306 due to incomplete urine collection. Group 4: $t_{1/2}$ and $CL_R$ could not be calculated for Subject 80405.
d Arithmetic mean ± standard deviation

**Table 7.**

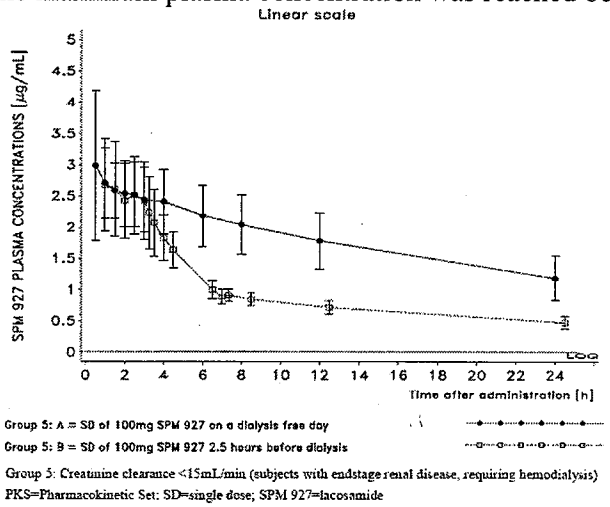
**ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for SPM 12809 - PKS**

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

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

***Part 2: ESRD patients on hemodialysis:***

*Lacosamide :*
Under a 4-hour dialysis starting 2.5 hours after dosing, $AUC_{(0-tz)}$ of LCM was approximately 50% lower in subjects with endstage renal disease (ESRD) receiving hemodialysis after a single oral dose of 100mg LCM (Treatment B) compared with dosing on a dialysis-free day (Treatment A) (Tables 8 and 9 and Figure 5). $C_{max}$ was less affected by dialysis than AUC, probably because the maximum plasma concentration was reached before the start of dialysis in most subjects.



Group 5: Creatinine clearance <15mL/min (subjects with endstage renal disease, requiring hemodialysis)
PKS=Pharmacokinetic Set; SD=single dose; SPM 927=lacosamide

**Figure 5. Mean plasma concentrations of lacosamide after single oral administration of 100mg lacosamide in subjects with endstage renal impairment on a dialysis-free day and under dialysis conditions.**

A comparison of the PK parameters $AUC_{(0-24)}$, $AUC_{(0-96)}$ (measured from 0 to 24 hours and extrapolated from 24 to 96 hours for subjects with ESRD), $C_{max}$, $t_{max}$, and $t_{1/2}$ of LCM for subjects with severe renal impairment with subjects with ESRD requiring dialysis in Part 2 indicated that the pharmacokinetics of LCM were similar in these 2 groups (Table 10). The approximation of $AUC_{(0-96)}$ for Group 5 resulted in an approximated mean value for subjects with endstage renal disease under non-dialysis conditions (Group 5/ Treatment A) that was very similar to the mean $AUC_{(0-96)}$ in subjects with severe renal impairment (Group 4). The extrapolated fraction of $AUC_{(0-96)}$ in Group 5 was between 19.7% and 63.8%. The PK parameters $C_{max}$, $t_{max}$, and $t_{1/2}$ were also similar in the 2 groups.

**Table 8. Pharmacokinetic parameters of lacosamide after Treatments A and B in subjects with end-stage renal disease, requiring dialysis.**

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

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

APPEARS THIS WAY
ON ORIGINAL

**Table 9.**

**ANOVA results for the ratio "Treatment B / Treatment A" for lacosamide - PKS**

| Parameter | Point estimate | 90% confidence interval |
|---|---|---|
| $AUC_{(0-tz)}$ | 0.5369 | (0.5060, 0.5697) |
| $C_{max}$ | 0.8757 | (0.7573, 1.0126) |

ANOVA=analysis of variance; PKS=Pharmacokinetic Set

Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis); Treatment B=single dose of 100mg lacosamide 2.5 hours before start of dialysis

**Table 10. Comparison of PK parameters of lacosamide from Group 4 and Group 5/Treatment A.**

| Parameter (unit) | Group 4 | Group 5/Treatment A |
|---|---|---|
| | Geometric mean (CV %) | |
| $AUC_{(0-24)}$ (µg/mL*h) | 45.31 (22.1) | 43.19 (20.2) [a] |
| $AUC_{(0-96)}$ (µg/mL*h) | 74.76 (26.9) [b] | 73.37 (26.3) [c] |
| $C_{max}$ (µg/mL) | 3.02 (23.3) | 3.18 (22.4) |
| $t_{max}$ (h) [d] | 1.00 (0.5-1.5) | 0.5 (0.50-4.0) |
| $t_{1/2}$ (h) | 18.30 (27.8) | 19.55 (19.4) |

CV=coefficient of variation;

Group 4=subjects with severe renal impairment; Group 5=subjects with endstage renal impairment, requiring dialysis; Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis)

[a] This parameter is shown as $AUC_{(0-tz)}$ in Table 3.2.2.1.

[b] This parameter is shown as $AUC_{(0-tz)}$ in Table 3.2.1.1.

[c] Estimation of the systemic exposure up to 96 hours after dosing by extrapolation of plasma concentration data.

[d] Median (range)

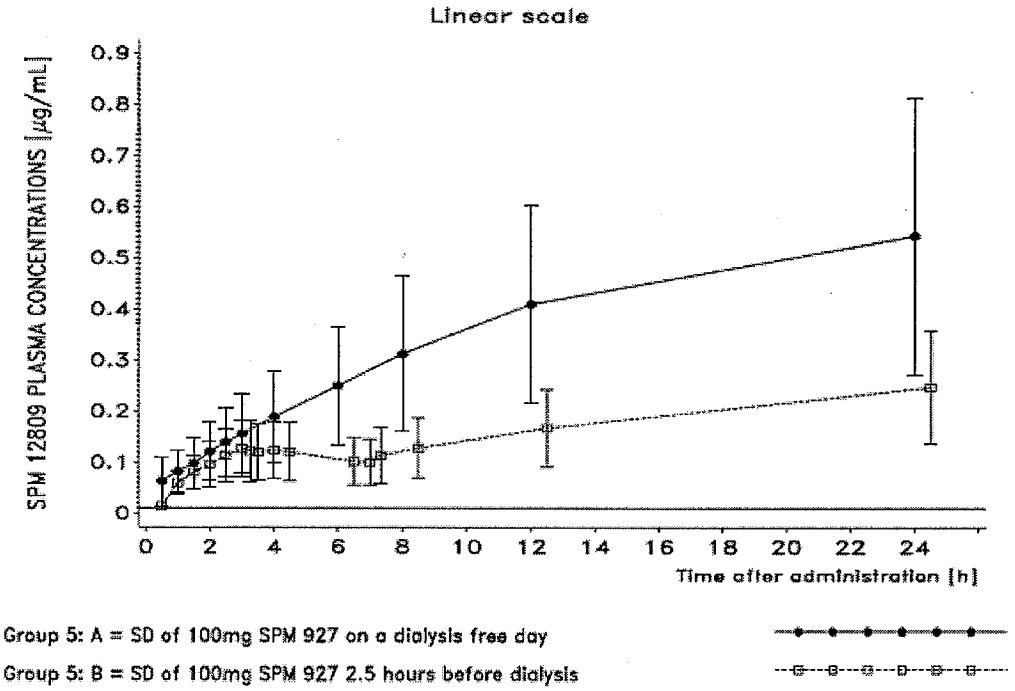
*SPM 12809:*

Mean plasma concentrations of SPM 12809 increased after dosing in both treatments and reached the maximum mean concentration within the observed sampling interval of 24 hours at the last measured time point after dosing. The maximum mean concentration observed at the end of the sampling interval of 24 hours was higher after Treatment A (0.54µg/mL) than after Treatment B (0.25µg/mL). With the start of dialysis 2.5 hours after dosing in Treatment B, the increase of plasma concentrations of the metabolite leveled off. Plasma concentrations of SPM 12809 started to increase again after the end of dialysis (ie, after the 6.5-hour time point).

As for the parent compound, $AUC_{(0-tz)}$ and $C_{max}$ (observed maximum concentration within the sampling interval of 24 hours) of SPM 12809 were lower when subjects with endstage renal

disease received hemodialysis after administration of lacosamide (Treatment B) compared with dosing on a dialysis-free day (Treatment A). The $C_{max}$ of SPM 12809 was 50% lower under dialysis conditions (Treatment B) than under non-dialysis conditions (Treatment A) (Tables 11 and 12 and Figure 6).

Mean values for $AUC_{(0-24)}$ of SPM 12809 were similar for subjects with endstagerenal disease under non-dialysis conditions (Group 5/Treatment A) and subjects with severe renal impairment (Group 4) (Table 13).




Group 5: Creatinine clearance <15mL/min (subjects with endstage renal disease, requiring hemodialysis)
SD=single dose; SPM 927=lacosamide

**Figure 6. Mean plasma concentrations of SPM 12809 in subjects with endstage renal impairment after single oral administration of 100mg lacosamide on a dialysis-free day and under dialysis condition.**

**Table 11. Pharmacokinetic parameters of SPM 12809 after Treatments A and B in subjects with endstage renal disease, requiring dialysis.**

| Parameter (unit) | Treatment A (N=8) | Treatment B (N=8) |
|---|---|---|
| | Geometric mean (CV %) | |
| $AUC_{(0-tz)}$ (µg/mL*h) | 6.63 (74.3) | 3.43 (68.5) |
| $AUC_{(0-tz)norm}$ (µg/mL*h*kg) | 469 (57.9) | 243 (53.1) |
| $C_{max}$ (µg/mL) [a] | 0.48 (69.5) | 0.22 (69.1) |
| $C_{max,norm}$ (µg/mL*kg) | 33.82 (51.2) | 15.35 (54.0) |
| Extraction rate (%) [b] | NA | 53.00±6.99 |
| $CL_{dial}$ t=4h (mL/min) | NA | 153.35 (15.2) |
| $CL_{dial}$ t=6.5h (mL/min) | NA | 148.51 (7.9) |
| Amount excreted by dialysis (mg) [b] | NA | 4.1±1.9 |

CV=coefficient of variation; NA=not applicable;
Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis); Treatment B=single dose of 100mg lacosamide 2.5 hours before start of dialysis
[a] Observed maximum concentration within the sampling interval of 24 hours
[b] Arithmetic mean±standard deviation

**Table 12.**

**ANOVA results for the ratio "Treatment B / Treatment A" for SPM 12809 - PKS**

| Parameter | Point estimate | 90% confidence interval |
|---|---|---|
| $AUC_{(0-tz)}$ | 0.5175 | (0.4071, 0.6579) |
| $C_{max}$ [a] | 0.4540 | (0.4009, 0.5142) |

ANOVA=analysis of variance; PKS=Pharmacokinetic Set
Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis); Treatment B=single dose of 100mg lacosamide 2.5 hours before start of dialysis
[a] Observed maximum concentration within the sampling interval of 24 hours

**Table 13. Comparison of PK parameters of lacosamide from Group 4 and Group 5/Treatment A.**

| Parameter (unit) | Group 4 | Group 5/Treatment A |
|---|---|---|
| | Geometric mean (CV %) | |
| $AUC_{(0-24)}$ (µg/mL*h) | 45.31 (22.1) | 43.19 (20.2) [a] |
| $AUC_{(0-96)}$ (µg/mL*h) | 74.76 (26.9) [b] | 73.37 (26.3) [c] |
| $C_{max}$ (µg/mL) | 3.02 (23.3) | 3.18 (22.4) |
| $t_{max}$ (h) [d] | 1.00 (0.5-1.5) | 0.5 (0.50-4.0) |
| $t_{1/2}$ (h) | 18.30 (27.8) | 19.55 (19.4) |


b(4)

CV=coefficient of variation;
Group 4=subjects with severe renal impairment; Group 5=subjects with endstage renal impairment, requiring dialysis; Treatment A=single dose of 100mg lacosamide on a dialysis-free day (1 day before dialysis)
a This parameter is shown as $AUC_{(0-tz)}$ in Table 3.2.2.1.
b This parameter is shown as $AUC_{(0-tz)}$ in Table 3.2.1.1.
c Estimation of the systemic exposure up to 96 hours after dosing by extrapolation of plasma concentration data.
d Median (range)

**Conclusions:**

- The systemic exposure of lacosamide (measured as $AUC_{(0-tz)}$ and $AUC_{(0-tz)norm}$) increased with increasing degree of renal impairment. Increases of 60% and 50% for $AUC_{(0-tz)}$ and $AUC_{(0-tz)norm}$, respectively, were observed in subjects with severe renal impairment compared with subjects with normal renal function. For $C_{max}$, only a slight difference was observed. The terminal half-life of lacosamide in plasma ($t_{1/2}$) was prolonged in subjects with severe renal impairment (approximately 18 hours) in comparison with healthy subjects (approximately 13 hours).

- Under a 4-hour dialysis starting 2.5 hours after dosing, $AUC_{(0-tz)}$ of LCM and SPM 12809 was approximately 50% lower in subjects with endstage renal disease (ESRD) receiving hemodialysis after a single oral dose of 100mg LCM (Treatment B) compared with dosing on a dialysis-free day (Treatment A).

- Due to the decreased plasma concentrations of lacosamide under dialysis conditions, dose adjustment has to be considered in clinical practice for patients under dialysis.

- In addition, hemodialysis can be considered as an effective treatment to reduce lacosamide plasma concentrations, for instance in case of overdosing.

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

*4.2.3.2 Hepatic Impairment— Study SP642: Open, non-randomized, group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 twice daily in male and female subjects with hepatic impairment compared with male and female healthy subjects following multiple-dose administration*

---

**Study Period:** April 6, 2004 to June 4, 2004
**Sample Analysis Period:** June 11, 2004 to August 23, 2004
**Analytical Site:** b(4)

b(4)

| | | |
|---|---|---|
| **Name of company:** SCHWARZ BIOSCIENCES GmbH | **Individual study table referring to part of the dossier** NA | *(For National Authority Use Only)* |
| **Name of Finished Product:** Not applicable | **Volume:** Not applicable | |
| **Name of Active Ingredient:** Lacosamide (SPM 927) | **Page:** Not applicable | |

**Title of trial**: Open, non-randomized, group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 twice daily in male and female subjects with hepatic impairment compared with male and female healthy subjects following multiple-dose administration

**Investigators**: [redacted]

**Trial site(s)**: [redacted]

A second planned site [redacted] was not initiated.

b(4)

**Publication (reference)**: None

| | |
|---|---|
| **Studied period (years)**: - | **Phase of development:** Phase 1 |
| **First subject enrolled**: 06 Apr 2004 | |
| **Last subject completed**: 04 Jun 2004 | |

**Objectives**: The objective of the trial was to evaluate the pharmacokinetics of unchanged lacosamide and its main metabolite SPM 12809 in subjects with hepatic impairment and (matched for age, body mass index, and gender) healthy subjects following multiple-dose administration of 100mg lacosamide twice daily. In addition, safety and tolerability of the treatment were evaluated.

**Methodology**: This was an open-label, non-randomized, non-controlled, parallel-group trial in which healthy subjects and subjects with moderate hepatic impairment received multiple doses of 100mg lacosamide twice daily between Day 1 and Day 5, followed by an Elimination phase until Day 9. For each subject the trial consisted of a Screening visit (Days -14 to -2), a 10-day in-house period (Days -1 to Day 9) and a Safety Follow-Up visit at least 14 days after last administration of trial medication.

**Number of subjects (planned and analyzed)**: Eight healthy male or female subjects (Group 1) and 8 male or female subjects with moderate hepatic impairment (Group 2) were planned to be enrolled in this trial. In each group, 6 male and 2 female subjects were enrolled and analyzed. All 16 subjects were valid for pharmacokinetic (PK) and safety analyses.

**Diagnosis and main criteria for inclusion**: Male or female Caucasian subjects between 18 and 65 years of age with a body mass index (BMI) between 20 and 34kg/m$^2$ (inclusive) were enrolled. Subjects in Group 1 were healthy, subjects in Group 2 had moderate hepatic impairment (Child-Pugh stage B). Subjects in Group 1 were matched for age, BMI, and gender to subjects in Group 2.

**Test product, dose and mode of administration, batch number**: 100mg lacosamide film-coated tablets, administered orally twice daily on Days 1-4 and once daily on Day 5.

Pack batch number: 20030203, Drug product batch number: 228920

**Duration of treatment**: 4.5 days

**Reference therapy, dose and mode of administration, batch number**: None

**Criteria for evaluation**:

Pharmacokinetics: Primary PK parameters of unchanged lacosamide and its main metabolite SPM 12809:

- $A_{e(0-12)ss}$ of lacosamide and SPM 12809 in urine
- $AUC_{(0-12)ss}$ and $AUC_{(0-12)ss,norm}$ of lacosamide and SPM 12809 in plasma
- Ratios "Group 2"/"Group 1" of these parameters

Secondary PK parameters of lacosamide and SPM 12809:

- $C_{max,ss}$, $C_{max,norm,ss}$, $t_{max,ss}$, and $t_{1/2}$ of lacosamide and SPM 12809 in plasma
- Ratios "Group 2"/"Group 1" of $C_{max,ss}$ and $C_{max,norm,ss}$

Safety:

- Subjective tolerability, adverse events (AEs)
- Determination of changes in laboratory parameters
- Influence on vital sign parameters (pulse rate, blood pressure) and electrocardiogram (ECG)

**Statistical methods**: The statistical analysis of PK parameters was carried out with the main purpose of deriving confidence intervals (CIs) for the ratios between subject groups. Descriptive statistics were displayed to provide an overview of the PK and safety results.

The primary PK parameters $AUC_{(0-12)ss}$, $AUC_{(0-12)ss,norm}$, and $A_{e(0-12)ss}$ of lacosamide and SPM 12809 as well as secondary PK parameters $C_{max,ss}$ and $C_{max,norm,ss}$ were analyzed assuming log-normally distributed data. The logarithms of $AUC_{(0-12)ss}$, $A_{e(0-12)ss}$, $C_{max,ss}$, and $C_{max,norm,ss}$ were analyzed using an explorative analysis of variance (ANOVA) including the factor "group." The ANOVA was calculated using the general linear models (GLM) procedure. The residuals of the ANOVA were examined for a normally distributed random error. In case of a significant deviation, the corresponding nonparametric analysis was performed. The results of this analysis were considered to be relevant. Based on these analyses, point estimates (least squares means [LS means]) and exploratory 90% CIs for the ratio "Group 2"/"Group 1" were calculated by retransformation of the logarithmic data using the root mean square of error of the ANOVA.

Pharmacokinetic characteristics ($t_{max}$ excluded) were summarized by the number of measurements, arithmetic mean, SD, coefficient of variation (CV), minimum, maximum, and median value and in addition by geometric mean, geometric SD (re-transformed SD of the logarithms), and geometric CV. The $t_{max}$ was described utilizing arithmetic mean, arithmetic SD, minimum, maximum, and median value. Means were only calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LOQ). For the calculation of the mean value, a data point below the LOQ was substituted by zero.

**Rationale for the study:** Previous ADME studies suggested that lacosamide undergoes metabolism. Impaired hepatic function may alter the pharmacokinetics of lacosomide and the dosage regimen may need to be adjusted in patients with hepatic impairment. Pharmacokinetic characterization in subjects with hepatic impairment would provide rational recommendations for dosing in such patients.

A multiple-dose design was chosen to ensure an accurate estimation of urine recovery of the unchanged drug and its main metabolite, SPM 12809.

**Dose selection:** A dose of 200 mg lacosamide daily (100 mg twice daily) for 4.5 days was selected that took into account that a reduced metabolism in subjects with hepatic impairment could lead to a possible increased exposure of lacosamide. The results from previous trials showed that doses up to 600 mg daily were tolerated.

**Sample Collection:**
For quantification of lacosamide and SPM 12809 in plasma, venous blood samples were drawn at the following time points:
• Pre-administration on Day 1 (blank)
• Pre-morning and pre-evening dose on Day 4 (trough values)
• 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, and 96 hours after the last administration of trial medication in the morning of Day 5

To determine renal excretion of lacosamide and its metabolite SPM 12809, urine was collected during the following collection periods:
• Pre-dose (blank) (Day 1)
• 0-12 hours post morning dose (Day 5)

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method using Positive Electrospray Ionization (ESI) and Selected Reaction Monitoring (SRM) in plasma (Validation Report No. —la279-1) and urine (Validation Report No. —la279-2). The LOQ for LCM in plasma was 0.1 µg/mL and in urine was 5 µg/mL. The LOQ for SPM 12809 in plasma was 0.02 µg/mL and in urine was 1 µg/mL. See tables below for summary of analytical assay data.

| Summary of the Assay Data - Plasma Analysis | | |
|---|---|---|
| | SPM 927 | O-Desmethyl-SPM 927 |
| Calibration range | 0.100 – 20.0 µg/mL | 0.0200 – 4.00 µg/mL |
| Lower Limit of Quantitation | 0.100 µg/mL | 0.0200 µg/mL |
| $r^2$ (mean) | 0.99959 | 0.99908 |
| % bias at the LOQ (n=7) | 0.2 | 0.5 |
| % cv at the LOQ (n=7) | 0.5 | 0.4 |
| % bias at the lowest QC (n=14) | 1.0 | 4.0 |
| % cv at the lowest QC (n=14) | 2.8 | 4.3 |

b(4)

| Summary of the Assay Data - Urine Analysis | | |
|---|---|---|
| | SPM 927 | O-Desmethyl-SPM 927 |
| Calibration range | 5.00 – 500 µg/mL | 1.00 – 100 µg/mL |
| Lower Limit of Quantitation | 5.00 µg/mL | 1.00 µg/mL |
| $r^2$ (mean) | 0.99794 | 0.99863 |
| % bias at the LOQ (n=2) | 0.9 | 1.3 |
| range | 0.0974 | 0.00154 |
| % bias at the lowest QC (n=4) | -0.7 | -4.9 |
| % cv at the lowest QC (n=4) | 0.8 | 1.0 |

**Subjects:** Sixteen subjects were enrolled in this trial: 8 healthy subjects (Group 1) and 8 subjects with moderate hepatic impairment (Group 2). All 16 subjects completed the trial and were valid for safety and PK analyses. In each group, 8 Caucasian subjects were enrolled. Six male subjects and 2 female subjects were enrolled in each group. Demographic data were similar for the 2 groups as shown in the table below.

**Table 1. Demographic data.**

| Parameter | Statistic | Group 1 (N=8) | Group 2 (N=8) |
|---|---|---|---|
| Gender<br>male<br>female | <br>N (%)<br>N (%) | <br>6 (75%)<br>2 (25%) | <br>6 (75%)<br>2 (25%) |
| Age (years) | Median (range) | 51.5 (42-55) | 52.0 (49-63) |
| Body mass index ($kg/m^2$) | Median (range) | 24.5 (20.6-26.7) | 23.1 (22.2-27.0) |
| Body height (m) | Median (range) | 1.71 (1.62-1.85) | 1.64 (1.50-1.75) |
| Body weight (kg) | Median (range) | 69.5 (54-90) | 62.5 (59-78) |

Group 1=healthy subjects; Group 2=subjects with moderate hepatic impairment (Child-Pugh stage B) with a liver vascular index ≤12cm/s (Subject 80209 was enrolled despite a slightly elevated value of 12.02cm/s) and a total Child-Pugh score between 7 and 9 points.

**Pharmacokinetic Results:**

*Plasma PK Profiles*

The trough levels indicate that steady state was reached on Day 4.

Plasma concentration-time profiles for lacosamide (LCM) amd SPM 12809 are shown in Figures 1 and 2.

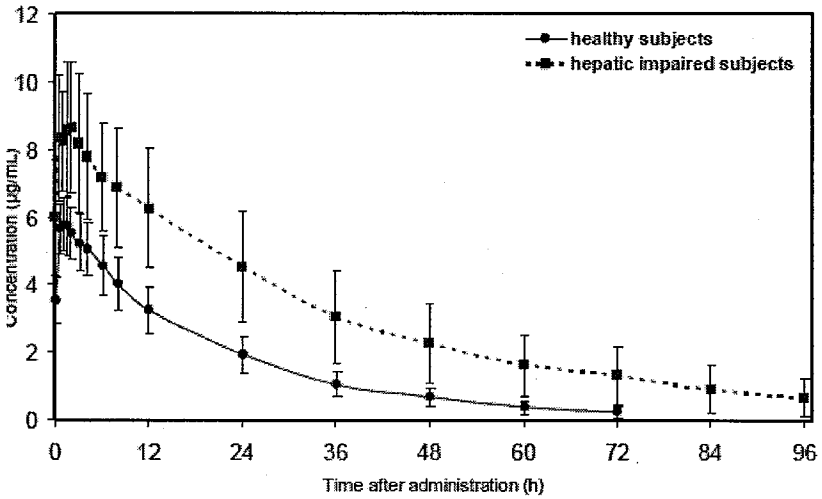



**Figure 1. Mean plasma concentrations of lacosamide at steady state starting on Day 5 (arithmetic mean±SD, linear scale).** Note: Means were only calculated if at least 2/3 of the individual data were >LOQ. In Group 1, less than 2/3 of individual data were >LOQ at the 84- and 96-hour time point.

In subjects with moderate hepatic impairment, higher maximum mean concentrations of LCM were reached compared to healthy subjects: Maximum mean concentrations were approximately 9µg/mL and 6µg/mL, respectively.

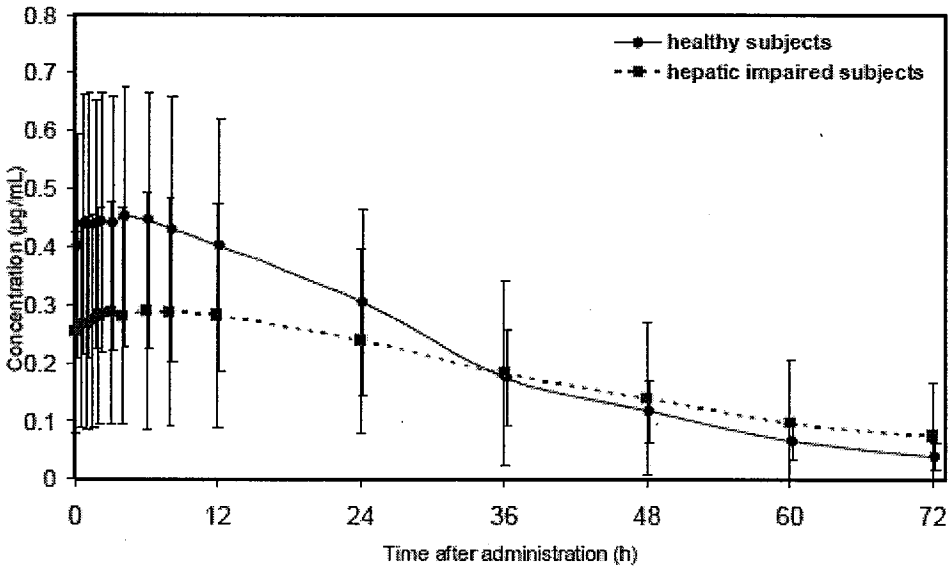



**Figure 2. Mean plasma concentrations of SPM 12809 at steady state starting on Day 5 (arithmetic mean±SD, linear scale).**

The maximum of mean plasma concentrations of SPM 12809 was reached within 4 to 6 hours. Healthy subjects reached higher maximum mean concentrations than subjects with moderate hepatic impairment: maximum mean concentrations were approximately 0.45µg/mL and 0.3µg/mL, respectively.

**Table 2. Pharmacokinetic parameters (geometric means and % coefficient of variation) after multiple oral administration of 100mg lacosamide twice daily at steady state (Day 5).**

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

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

For lacosamide, $AUC_{(0-12)ss}$ and $C_{max,ss}$ were higher in subjects with moderate hepatic impairment than in healthy subjects: Values for $AUC_{(0-12)ss}$ were 1.6-fold higher (1.5-fold after body-weight normalization) and values for $C_{max,ss}$ were 1.5-fold higher (1.4-fold after body-weight normalization). There was no difference in the time of observed maximum at steady state ($t_{max,ss}$) of lacosamide between the 2 groups. The terminal half-life ($t_{1/2}$) of lacosamide was prolonged 1.6-fold in subjects with moderate hepatic impairment.

The amount of lacosamide excreted into urine within 12 hours after application at steady state ($A_{e(0-12)ss}$) was lower in subjects with moderate hepatic impairment than in healthy subjects (factor: 0.8).

**Table 3. Summary of analysis of variance of log-transformed pharmacokinetic parameters for lacosamide and SPM 12809 at steady state (Day 5) for the comparison "Group 2"/"Group 1".**

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

$AUC_{(0-12)ss}$ was 61% higher in subjects with hepatic impairment compared to healthy subjects. After body-weight normalization, $AUC_{(0-12)ss}$ was still increased by 47%. $C_{max,ss}$ was 50% higher in subjects with hepatic impairment (37% after body-weight normalization).

An analysis of the relationship between PK parameters and the subjects' renal function was performed to evaluate whether the renal function has an influence on the pharmacokinetics of lacosamide. The analysis was done because lacosamide is eliminated primarily via renal excretory mechanisms and a wide range of calculated creatinine clearances was observed in this trial (36-196mL/min at steady state). As of note, the estimated $CL_{Cr}$ according to Cockcroft and Gault was comparable in the 2 groups. The GFR estimated using the MDRD formula was slightly higher in subjects with moderate hepatic impairment (Group 2) compared to healthy subjects (Group 1): in Group 2, the median GFR value was 110 mL/min on Day 1 and 100 mL/min on Day 5 compared to 90mL/min on Days 1 and 5 in Group 1. No relevant changes from Baseline were observed during treatment with lacosamide.

The calculated $CL_{Cr}$ was based on 24-hour urine sampling of creatinine. The reviewer questioned the accuracy of the calculated creatinine clearance in the study because large changes were observed for some subjects between Day 1 and Day 5 (Table 4). For example, Subject 80204 had calculated CLcr of 57 mL/min on Day 1, and 181 mL/min on Day 5 and Subject 80214 had calculated CLcr of 384 mL/min on Day 1 and 42 mL/min on Day 5. In addition, Subject 213 should have been excluded because CLcr <50 mL/min at the baseline.

APPEARS THIS WAY
ON ORIGINAL

**Table 4. Calculated creatinine clearance (0-24 hr) (mL/min) in healthy subjects and subjects with moderate hepatic impairment.**

| Group 1 (Normal) | Day 1 | Day 5* | Group 2 (Moderate Hepatic Impairment) | Day 1 | Day 5* |
|---|---|---|---|---|---|
| 80201 | 164 | 151 | 80209 | 65 | 100 |
| 80202 | 203 | 139 | 80210 | 128 | 156 |
| 80203 | 141 | 126 | 80211 | 73 | 89 |
| 80204 | **57** | **181** | 80212 | 54 | 53 |
| 80205 | 147 | 157 | 80213 | 21 | 36 |
| 80206 | 121 | 125 | 80214 | **384** | **42** |
| 80207 | 113 | 141 | 80215 | 214 | 196 |
| 80208 | 86 | 147 | 80216 | 155 | 145 |
| **Mean CLcr (Range) (mL/min)** | | | | | |
| | 131 (57-203) | 144 (125-181) | | 100 (21-384) | 94 (36-196) |

* Determined by combination of Day 5/0-12h and Day 5/12-24h.
Group 1=healthy subjects; Group 2=subjects with moderate hepatic impairment (Child-Pugh stage B)

When based on calculated CLcr for renal function characterization, all subjects in Group 1 had normal renal function on Day 5 and 3 subjects (Subjects 80212, 80213, and 802144) in Group 2 had impaired renal function. The figure below shows the relationship between $AUC_{(0\text{-}12)ss,norm}$ of lacosamide at steady state and the calculated $CL_{Cr}$ of the subjects (Day 5). The figure shows that reduced $CL_{Cr}$ may contribute to the higher $AUC_{(0\text{-}12)ss,norm}$ of lacosamide in a subset of subjects (3 subjects) with hepatic impairment.

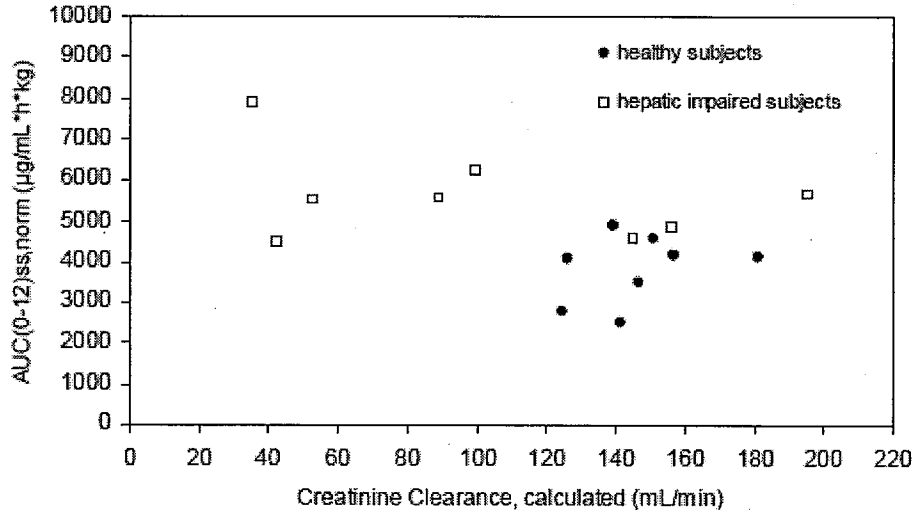



**Figure 3. Relationship between $AUC_{(0\text{-}12)ss,norm}$ of lacosamide and calculated creatinine clearance at steady state (Day 5).**

When compared AUC and Cmax of 5 subjects who had moderate hepatic impairment and whose renal function was considered normal based on calculated renal function to those who had normal hepatic and renal function, AUC was 50% higher and Camx was 40% higher in the prior group (Table 5).

**Table 5. PK Parameter Comparison.**

| | **Group 1 (N=8)** | **Group 2 (N=8)** | **Group 2 (N=5) (excluding Subjects 80212, 80213, and 802144)** | **Group 2 (N=3) (Subjects 80212, 80213, and 802144)** |
|---|---|---|---|---|
| AUC(0-12) (μg/mL*hr) | 54 ± 9 | 88 ± 21 | 81 ± 11 | 99 ± 31 |
| Percent Difference to Normal | - | 63% ↑ | 50% ↑ | 83% ↑ |
| Cmax (μg/mL) | 5.9 ± 5.8 | 8.9 ± 1.9 | 8.2 ± 0.8 | 10 ± 3 |
| Percent Difference to Normal | | 52% ↑ | 40% ↑ | 70% ↑ |

**Safety Results:** No death or serious AE occurred during the course of the trial. Five subjects (3 healthy subjects and 2 subjects with moderate hepatic impairment) reported 6 treatment-emergent AEs.

**Conclusions:**
Plasma concentrations of lacosamide were approximately 50-60% higher in the subjects with hepatic impairment compared to healthy subjects. Plasma concentrations of the main metabolite of lacosamide, SPM 12809, were approximately 40-50% lower in subjects with hepatic impairment compared to healthy subjects.

The data indicate that hepatic metabolism is involved in the metabolism of lacosamide. Higher plasma concentrations of lacosamide in 3 subjects with moderate hepatic impairment may be partially caused by a reduced renal function compared to healthy subjects. Exposure of lacosamide in the remaining 5 subjects with moderate hepatic impairment was 50% higher than healthy subjects. The highest dose in moderate hepatic impairment patients should be reduced to — of the highest doses recommended in patients who have normal hepatic function for comparable lacosamide exposure. b(4)

PK of lacosamide has not been studied in mild or severe hepatic impairment patients. Same recommendation would be given to the mild and moderate hepatic impairment patients and lacosamide will be contraindicated in patients with severe hepatic impairment.

*4.2.3.3 Age and Gender— Study SP620: Double-blind, placebo-controlled, parallel group trial to evaluate the pharmacokinetics and tolerability of SPM 927 (harkoseride) following single and multiple oral administration to 48 healthy Caucasian subjects differing in age and gender*

---

**Study Period:** June 28, 2001 to August 31, 2001
**Sample Analysis Period:** August 31, 2001 to October 23, 2001
**Analytical Site:** b(4)

| |
|---|
| **Title of the study:**<br>Double-blind, placebo-controlled, parallel group trial to evaluate the pharmacokinetics and tolerability of SPM 927 (harkoseride) following single and multiple oral administration to 48 healthy Caucasian subjects differing in age and gender |
| **Investigator:** b(4) |
| **Study centre(s):** b(4) |
| **Publication (reference):**<br>n.a. |

| **Studied period:** | **Clinical Phase:** |
|---|---|
| 28 June 2001 – 31 August 2001 | Phase I |

**Objectives:**

*Primary objectives:*

To determine the pharmacokinetics of unchanged SPM 927 in plasma and urine in healthy elderly male and female subjects in comparison to young healthy male subjects and to evaluate gender difference in the pharmacokinetics based on AUC(0-∞) or $AUC_{SS}$ and $C_{max}$ calculated from plasma samples as well as amount excreted in the urine (Ae) calculated from urine samples, both after single dosing and at steady state.

*Secondary objectives:*

To determine pharmacokinetic parameters AUC(0-$t_z$), $t_{max}$, $t_{½}$, $CL_{tot}/f$ from plasma samples after single dosing, $t_{max}$, $t_{½}$, $C_{min}$, $CL_{tot}/f$ from plasma samples at steady state and $CL_R$ from urine samples after single dosing and at steady state. To determine safety and tolerability based on adverse events, changes in vital signs, physical examination, 12-lead ECG parameters, hematology, and clinical chemistry parameters. To determine potential metabolites in urine and plasma, if methods are available.

**Methodology/Design:**

Double-blind, placebo-controlled, parallel groups, single and multiple administration, young and elderly healthy subjects

**Number of subjects (total for each age and sex):**

86 subjects were screened, 51 subjects were included, and 4 subjects dropped out.

15 Elderly males (11 received SPM 927, 4 received placebo), aged 65 years and older

16 Elderly females (12 received SPM 927, 4 received placebo), aged 65 years and older

16 Young males (12 received SPM 927, 4 received placebo), aged 18-45 years

completed the study.

**Diagnosis and criteria for inclusion:**

Subjects were male or female Caucasian. Male subjects are aged between 18-45 years (inclusive) or are aged 65 years and older, female subjects are aged 65 years and older. Subject is of normal body-weight as determined by the body mass index ranging between 19 to 30 kg/m$^2$.

**Test product, dose, mode of administration, batch No.:**

| | |
|---|---|
| Day 1, 8: | 100 mg SPM 927 once daily oral administration, single dose (in the morning) |
| Day 4, 5, 6, 7: | 100 mg SPM 927 b.i.d. oral administration, multiple dose (one administration in the morning and one in the evening, respectively) |
| Batch-No.: | 217860 |

**Reference therapy, dose, mode of administration, batch No.:**

There was a corresponding placebo control reference therapy:

| | |
|---|---|
| Day 1/Day 8: | placebo o.d. oral treatment, single dose (in the morning) |
| Day 4 to Day 7: | placebo b.i.d. oral treatment, multiple dose (one administration in the morning and one in the evening, respectively) |
| Batch-No.: | 215500 |

**Duration of treatment:**

Single dose treatment:

100 mg SPM 927 once daily oral treatment or placebo on Day 1 in the morning

Multiple dose treatment:

on Days 4 to 7 100 mg SPM 927 or placebo oral treatment b.i.d. and 100 mg SPM 927 or placebo once daily oral treatment in the morning of Day 8

**Criteria for evaluation:**

$AUC(0\text{-}\infty)$, $AUC_{ss}$, $C_{max}$ and Ae of SPM 927 were considered as primary parameters, evaluated separately after single dosing (day 1) and at steady-state conditions (day 8).

$t_{1/2}$ and $t_{max}$ of SPM 927 and the corresponding pharmacokinetic parameters of the main metabolite O-desmethyl-SPM 927 were also compared statistically between subject groups.

Further secondary pharmacokinetic parameters which were calculated but were not compared between study groups are $CL_{tot}/f$ and $CL_R$.

Safety data (AE incidence, changes in vital signs, physical examination, 12-lead ECG parameters, hematology, and clinical chemistry) were evaluated descriptively.

**Statistical methods:**

An analysis of variance was applied to ln(AUC), $ln(C_{max})$, $ln(t_{½})$ and Ae, Mann-Whitney U-tests for $t_{max}$. Between-group ratios or differences were estimated with 90% confidence intervals.

**Dose selection:** In this study a dose of 100 mg bid was studied. The proposed therapeutic doses are 50-[redacted] mg twice daily. b(4)

A young female group was not included because preclinical evaluation of potential teratogenic effects had not been completed at the time of the trial.

**Formulation:** 100 mg film-coated tablet

**Sample Collection:**

Blood sampling

Day 1 – Day 11

For the determination of SPM 927, 33 samples were drawn at the following times:

0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 132, 144, 156, hours following first dose, pre-dose on day 8 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours following last dose on morning of day 8.

Urine collection

For the evaluation of the excretion of SPM 927 in urine, urine was collected during the following time intervals:

Day 1 and Day 8: 0 (pre-dose voiding), 0-6, 6-12 and 12-24 hours after the respective dose, i.e. 3 samples/subject/day. The predose sample on Day 8 was not analyzed and was discarded.

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method using Positive Electrospray Ionization (ESI) and Selected Reaction Monitoring (SRM) in plasma (Validation Report No. [redacted]-la279-1) and urine (Validation Report No. [redacted]-la279-2). The LOQ for LCM in plasma was 0.1 µg/mL and in urine was 5 µg/mL. The LOQ for SPM 12809 in plasma was 0.02 µg/mL and in urine was 1 µg/mL. See tables below for summary of analytical assay data. b(4)

**Table 1. Summary of Assay Data-Plasma Analysis.**

| | LCM | SPM 12809 |
|---|---|---|
| Calibration range | 0.100 – 20.0 µg/mL | 0.0200 – 4.00 µg/mL |
| Lower Limit of Quantitation | 0.100 µg/mL | 0.0200 µg/mL |
| $r^2$ (mean) | 0.99533 | 0.99181 |
| % bias at the LOQ (n=19) | -1.0 | 0.0 |
| % cv at the LOQ (n=19) | 3.0 | 3.5 |
| % bias at the lowest QC (n=38) | -0.5 | -2.0 (n=35) |
| % cv at the lowest QC (n=38) | 7.9 | 9.7 (n=35) |

**Table 2. Summary of Assay Data-Urine Analysis.**

| | LCM | SPM 12809 |
|---|---|---|
| Calibration range | 5.00 – 500 µg/mL | 1.00 – 100 µg/mL |
| Lower Limit of Quantitation | 5.00 µg/mL | 1.00 µg/mL |
| $r^2$ (mean) | 0.99192 | 0.98876 |
| % bias at the LOQ (n=5) | -3.0 | 0.7 |
| % cv at the LOQ (n=5) | 2.9 | 2.6 |
| % bias at the lowest QC (n=12) | -4.1 | 2.7 |
| % cv at the lowest QC (n=12) | 7.3 | 10.0 |

**Subjects:**

**Table 3. Demographic data.**

| | | Elderly males | | Elderly females | | Young males | |
|---|---|---|---|---|---|---|---|
| | | SPM 927 (n=12) | placebo (n=5) | SPM 927 (n=12) | placebo (n=4) | SPM 927 (n=12) | placebo (n=5) |
| Age | [years] | 71.3 | 73.4 | 69.7 | 66.5 | 36.8 | 34.0 |
| Height | [cm] | 171.8 | 177.8 | 161.5 | 162.3 | 178.4 | 175.6 |
| Weight | [kg] | 76.9 | 87.9 | 66.0 | 66.3 | 80.5 | 71.1 |
| BMI | [kg/m²] | 25.9 | 27.8 | 25.2 | 25.1 | 25.2 | 23.1 |

17 elderly males were administered the study drug and 15 elderly males completed the study. 16 elderly females were administered and completed the study. 17 young males were administered and 16 young males completed the trial. 15 elderly males, 16 elderly females, and 16 young males are valid for complete analysis.

Subject # 8006 dropped out from the study on 20 July 2001, study day 4, because of an increase in blood pressure prior to dosing in the morning.

Subject # 8008 dropped out from the study on 22 July 2001, study day 6, because of an arrhythmia secondary to atrial fibrillation.

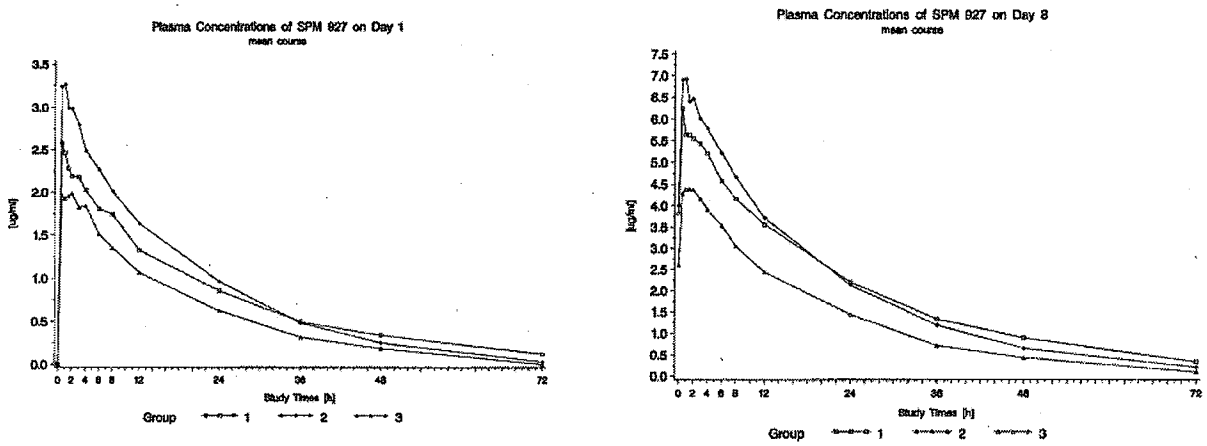
Subject # 8037 dropped out from the study on study day 1 because of private reasons.

Subject # 8016 dropped out of the study on 17 August 2001, study day 1 before dosing, because extrasytoles occurred during the pre-dose ECGs.

Thus, 4 subjects in total dropped out. 3 dropped out because of a medical reason and one who dropped out because of a private reason („non-completer").

**Pharmacokinetic Results:**

*Plasma PK Profiles for LCM*




Day 1 Day 8

**Figure 1. Mean plasma concentrations of lacosamide on Day 1 and at steady state starting on Day 8.** Group 1=elderly males; Group 2=elderly females; Group 3=young males

*Single dose:*

**Table 4.**

**Geometric Means and geometric CVs of AUC(0-∞), $C_{max}$ and $t_{1/2}$, medians and ranges for $t_{max}$ of SPM 927 after single dosing (Day 1)**

n = 12 subjets, each group

| Group | AUC(0-∞) [µg*h/mL] | $C_{max}$ [µg/mL] | $t_{1/2}$ [h] | $t_{max}$ [h] |
|---|---|---|---|---|
| Elderly males | 55.2 / 24%* | 2.77 / 22% | 16.7 / 22%* | 0.5 / 0.5-1.5 |
| Elderly females | 60.5 / 14% | 3.40 / 19% | 13.1 / 17% | 1.0 / 0.5-2 |
| Young males | 40.8 / 15% | 2.16 / 24% | 14.1 / 23% | 1.0 / 0.5-2 |

* : n=11

**Table 5.**

**Means and CVs of Ae and geometric means and geometric CV of $CL_R$ for SPM 927 after single dosing**

n = 12 subjets, each group

| Group | Ae [mg] | $CL_R$ [mL/min] |
|---|---|---|
| Elderly males | 21.0 / 30% | 9.7 / 29% |
| Elderly females | 24.1 / 39% | 8.8 / 37% |
| Young males | 17.7 / 37% | 9.7 / 43% |

Table 6.

**Group Ratios or differences (*) and 90% Confidence Intervals for Pharmacokinetic Parameters of SPM 927 after single dosing (Day 1)**
n = 12 subjets, each group

| Parameter | 1 / 3 | 2 / 1 | 2 / 3 |
|---|---|---|---|
| AUC(0-∞) geometric | 135.47% (119%,154%) | 109.50% (96%,124%) | 148.34% (131%,168%) |
| $C_{max}$ geometric | 128.58% (111%,149%) | 122.62% (106%,142%) | 157.66% (136%,183%) |
| $t_{max}$* arithmetic | -0.25h (-1h, ±0h) | ±0h (±0h, +0.5h) | ±0h (-0.5h, +0.5h) |
| $t_{1/2}$ geometric | 118.02% (102%,136%) | 78.63% (68%,91%) | 92.79% (81%,107%) |
| Ae* arithmetic | +18.32% (-11%,+48%) | +3.20% (-10%,+40%) | +36.36% (+7%,+66%) |

1 = elderly males, 2 = elderly females, 3 = young males

*Steady-State:*

Table 7.

**Geometric Means and geometric CVs of $AUC_{ss}$, $C_{max}$ and $t_{1/2}$, medians and ranges for $t_{max}$ of SPM 927 at steady-state (Day 8)**

| Group | $AUC_{ss}$ [µg*h/mL] | $C_{max}$ [µg/mL] | $t_{1/2}$ [h] | $t_{max}$ [h] |
|---|---|---|---|---|
| Elderly males* | 54.7 / 23% | 6.20 / 20% | 16.7 / 22% | 0.5 / 0.5-2 |
| Elderly females | 61.9 / 14% | 7.36 / 12% | 13.8 / 22% | 0.75 / 0.5-2 |
| Young males | 41.2 / 14% | 4.82 / 10% | 14.2 / 11% | 1.0 / 0.5-3 |

n = 12 or * 11

Table 8.

**Means and CVs of amounts excreted in the urine Ae(0-12) and geometric means and geometric CV of renal clearance $CL_R$ for SPM 927 at steady-state**

| Group | Ae(0-12) [mg] | $CL_R$ [mL/min] |
|---|---|---|
| Elderly males* | 34.5 / 37% | 9.7 / 57% |
| Elderly females | 41.5 / 54% | 10.2 / 32% |
| Young males | 33.0 / 31% | 12.0 / 68% |

n= 12 or * 11

Table 9.

**Group Ratios or differences (*) and 90% Confidence Intervals for Pharmacokinetic Parameters of SPM 927 at steady-state (Day 8)**

| Parameter | 1 / 3 | 2 / 1 | 2 / 3 |
|---|---|---|---|
| $AUC_{ss}$ geometric | 132.57% (118%, 150%) | 113.28% (100%, 128%) | 150.17% (133%, 169%) |
| $C_{max}$ geometric | 128.70% (116%, 143%) | 118.64% (107%, 131%) | 152.69% (138%, 169%) |
| $t_{max}$* arithmetic | -0.5h (-1h, ±0h) | ±0h (±0h, 0.5h) | -0.5h (-1h, ±0h) |
| $t_{1/2}$ geometric | 117.32% (103%, 134%) | 82.91% (73%, 94%) | 97.27% (86%, 110%) |
| Ae* arithmetic | +10.21% (-11%, +30%) | -1.78% (-22%, +26%) | +5.64% (-13%, +27%) |

1 = elderly males (n = 11), 2 = elderly females (n = 12), 3 = young males (n = 12)

When the parameters AUC and $C_{max}$ are adjusted per kg body weight the observed differences between the groups decrease.

After adjustment, elderly males and females are statistically indistinguishable but there still were significant differences between age groups.

Table 10.

**Group ratios and 90% confidence intervals of parameters corrected for dose per kg body weight**

| Parameter | 1/3 | 2/1 | 2/3 |
|---|---|---|---|
| $AUC_{norm}$ | 126% 108-147% | 98% 84-114% | 123% 106-143% |
| $C_{max,norm}$ | 122% 108-138% | 102% 90-116% | 125% 111-141% |

1 = elderly males (n = 11), 2 = elderly females (n = 12), 3 = young males (n = 12)

**Safety Results:**

No deaths occurred during this study. Two subjects experienced serious adverse events.

Subject no. 8006, an elderly male of group 1, SPM 927 treatment, had an increase in blood pressure to 210/110 mmHg prior to the planned first multiple dose dosage on study day 4. The blood pressure had been normal during the eligibility assessment as well as before dosing and in the measurements after dosing of day 1. The subject was therefore not dosed and was withdrawn from the study. His subjective well-being and

The ECG-recording of subject no. 8008, an elderly male in group 4, receiving placebo treatment showed an arrhythmia secondary to atrial fibrillation on day 6 before the next planned multiple dose administration. Blood pressure, heart rate and the subjective well-being were unaffected. The subject was excluded from further study treatment and withdrawn from the study on the same day. The arrhythmia secondary to atrial

**Conclusions:**
$AUC_{(0-\infty)}$ or $AUC_{\tau,ss}$, $C_{max}$, and $A_e$ were higher in elderly male and female subjects compared with young male subjects. If age is considered, elderly male subjects showed ~30% higher AUC than young male subjects. If gender is considered, elderly female subjects showed ~15% higher AUC than elderly male subjects. When taking body weight differences into considerations, the difference between genders decreased, however, there is still 20-25% difference between elderly and young subjects. Because of the high solubility of LCM in water, an increased LCM concentration in elderly subjects could result from the reduced body water in this age group. In addition, an influence of reduced renal function in elderly subjects could not be excluded.

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

*4.2.3.4 Race— Study SP661: Randomized, double-blind, placebo-controlled, parallel-group, Phase 1 trial to evaluate the pharmacokinetics, safety, and tolerability following multiple-dose oral treatment of 200mg SPM 927 in healthy male White, Black, and Asian subjects*

---

| | |
|---|---|
| **Study Period:** | August 14, 2004 to October 1, 2004 |
| **Sample Analysis Period:** | October 19, 2004 to November 18, 2004 |
| **Analytical Site:** | SCHWARZ BIOSCIENCES GmbH, Department of Bioanalytics, Alfred-Nobel-Straße 10, 40789 Monheim am Rhein, Germany |

| | |
|---|---|
| **Title of trial**: Randomized, double-blind, placebo-controlled, parallel-group, Phase 1 trial to evaluate the pharmacokinetics, safety, and tolerability following multiple-dose oral treatment of 200mg SPM 927 in healthy male White, Black, and Asian subjects | |
| **Investigators**: [redacted] | |
| **Trial site(s)**: [redacted] | |
| **Publication (reference)**: None | |
| **Studied period (years)**: -<br>**First subject enrolled**: 14 Aug 2004<br>**Last subject completed**: 01 Oct 2004 | **Phase of development**: Phase 1 |
| **Objectives**: The objective of the trial was to evaluate the pharmacokinetics of lacosamide (SPM 927) in subjects from 3 different ethnic groups following multiple-dose administration of 200mg lacosamide twice daily for 3.5 days. A comparison of pharmacokinetic (PK) parameters was performed to assess whether the affiliation to different ethnic groups had an influence on the metabolism of lacosamide.<br>In addition, safety and tolerability of the treatment were evaluated. | |
| **Methodology**: This was a randomized, double-blind, placebo-controlled, parallel-group Phase 1 trial exploring the pharmacokinetics, safety, and tolerability of orally administered lacosamide in different ethnic groups. Thirty-six subjects (12 from each ethnic group) received 200mg lacosamide twice daily and 12 subjects (4 from each ethnic group) received matching placebo treatment. Total duration of the trial for each subject from Eligibility Assessment to the Safety Follow-Up Visit was approximately 4 to 5 weeks including 3.5 days of treatment. | |
| **Number of subjects (planned and analyzed)**: As planned, 48 subjects (16 from each ethnic group) were enrolled in the trial. All 48 subjects were valid for PK and safety analysis. | |
| **Diagnosis and main criteria for inclusion**: Subjects were 18- to 45-year-old, healthy male subjects from 3 different ethnic groups (Asian, Black, and White). | |
| **Test product, dose and mode of administration, batch number**: Film-coated tablets of 100mg lacosamide, administered orally (two 100mg tablets per dose); drug product batch number: 231120; pack batch number: 066104070001. | |
| **Duration of treatment**: 3.5 days | |
| **Reference therapy, dose and mode of administration, batch number**: Film-coated placebo tablets matched to lacosamide; drug product batch number: 231960; pack batch number: 066104070001. | |

b(4)

APPEARS THIS WAY
ON ORIGINAL

| |
|---|
| **Criteria for evaluation:**<br>**Pharmacokinetics**: Primary PK parameters of lacosamide were:<br>• $AUC_{\tau,ss}$, $C_{max,ss}$, and body-weight normalized parameters $AUC_{\tau,ss,norm}$ and $C_{max,ss,norm}$<br>Further PK parameters of lacosamide and the main metabolite SPM 12809 were:<br>• C(t) of lacosamide at different time points t, $t_{1/2}$, $t_{max}$, MRT, CL/f, $A_e$, $CL_R$, $C_{trough}$, and $C_{min}$ of lacosamide and SPM 12809<br>• $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max,ss}$, $C_{max,ss,norm}$ of SPM 12809<br>**Safety**:<br>• Subject tolerability, adverse events (AEs)<br>• Determination of changes in laboratory parameters relevant to safety<br>• Influence on vital parameters (pulse rate, blood pressure, electrocardiogram [ECG]) |
| **Statistical methods**: A formal statistical sample size estimation was not performed due to the exploratory character of the trial. Descriptive statistics were displayed by treatment and by ethnic group to provide an overview of the PK and safety results. To investigate the influence of ethnic origin on the pharmacokinetics of lacosamide, log-transformed primary PK parameters $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max,ss}$, and $C_{max,ss,norm}$ were analyzed using an explorative analysis of variance (ANOVA) including the factor "ethnic group." |

**Study Rationale:** Lacosamide is to be registered globally. Therefore, pharmacokinetics and relative bioavailability as well as safety and tolerability in and between different ethnic groups were evaluated in the present study following administration of 200 mg lacosamide twice daily. The dosage represents a clinically relevant dose. The comparison of the ethnic groups was performed under steady-state conditions because the typical dosing for patients with epilepsy or neuropathic pain is a multipledose treatment.

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method using Positive Electrospray Ionization (ESI) and Selected Reaction Monitoring (SRM) in plasma (Validation Report No. BA 583-03) and urine (Validation Report No. 585-02). The LOQ for LCM and SPM 12809 in plasma was 0.01 µg/mL and in urine was 0.2 µg/mL. See tables below for summary of analytical assay data.

Plasma assay:

**Parameters of the assayed standard concentrations and the calibration curves**

| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of correlation 'r' | Precision of slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.4 - 8.6 | 97.6 - 104.0 | 0.9998 | 8.9% |
| | | | 0.9999 | 8.2% |
| SPM 12809 | 0.2 - 7.2 | 93.5 - 102.4 | 0.9999 | 7.5% |

**Parameters of the QC samples**

| Reference compounds | Precision [%] | Accuracy [%] |
|---|---|---|
| SPM 927 | 3.2 - 6.2 | 99.1 - 102.9 |
| SPM 12809 | 4.2 - 6.2 | 99.8 - 100.8 |

QC: 20, 1000 or 5000 ng/mL

Urine assay:

**Parameters of the assayed standard concentrations and the calibration curves**

| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of correlation 'r' | Precision of slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.5 - 4.0 | 95.3 - 107.1 | 0.99903 | 1.9% |
| SPM 12809 | 1.7 - 9.1 | 94.3 - 107.6 | 0.99837 | 1.0% |

**Parameters of the QC samples**

| Reference compounds | Precision [%] | Accuracy [%] |
|---|---|---|
| SPM 927 | 2.1 - 9.5 | 95.8 - 106.9 |
| SPM 12809 | 1.8 - 7.6 | 98.0 - 104.8 |

QC: 50, 2000 or 15000 ng/0.1 mL

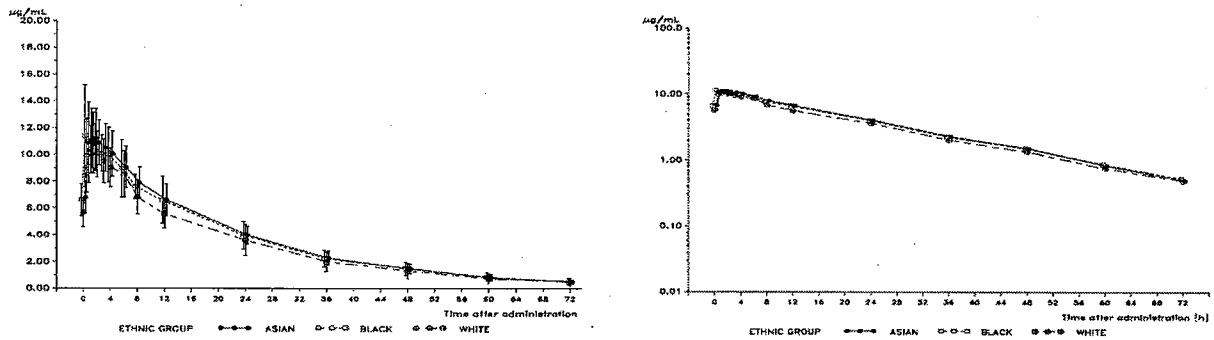
**Subjects:** Forty-eight healthy male subjects (16 Asian, 16 Black, and 16 White) were enrolled in the trial and randomized to receive 200 mg lacosamide twice daily (12 subjects from each ethnic group) or matching placebo treatment (4 subjects from each ethnic group). White subjects had a slightly higher body weight compared to Asian and Black subjects (Table 1).

**Table 1. Demographic data.**

| Parameter (unit) | Statistic | Asian (N=16) | Black (N=16) | White (N=16) |
|---|---|---|---|---|
| Age (years) | Mean±SD (Range) | 28.4±6.8 (20-41) | 24.6±5.6 (19-39) | 28.1±8.8 (19-45) |
| Body height (cm) | | 175.1±8.2 (162-188) | 172.6±6.7 (156-180) | 178.9±5.5 (168-190) |
| Body mass index ($kg/m^2$) | | 23.09±1.72 (20.5-26.3) | 22.86±1.71 (19.5-26.5) | 24.06±2.89 (19.7-28.9) |
| Body weight (kg) | | 70.91±8.38 (58.0-89.0) | 68.09±5.70 (54.5-81.0) | 76.95±9.76 (62.5-97.7) |

**Pharmacokinetic Results:**
The predose concentrations of lacosamide show that steady-state conditions were achieved in all ethnic groups on Day 4.

*Plasma PK Profiles for LCM*
Mean plasma concentration-time curves of lacosamide are shown in Figure 1.




Linear Semi-log

**Figure 1. Mean plasma concentrations of lacosamide after multiple oral administration of 200mg lacosamide at steady state (Day 4) (N=12 for each ethnic group).**

**Table 2. Pharmacokinetic parameters (geometric mean and CV [%]) of lacosamide.**

| Parameter (unit) | Lacosamide | | |
|---|---|---|---|
| | Asian (N=12) | Black (N=12) | White (N=12) |
| $AUC_{\tau,ss}$ (µg/mL*h) | 105.87 (15.6) | 104.79 (19.2) | 94.95 (17.3) |
| $AUC_{\tau,ss,norm}$ (µg/mL*h*kg) | 7358 (15.6) | 7327 (18.3) | 7322 (20.5) |
| $C_{max,ss}$ (µg/mL) | 12.03 (16.8) | 11.82 (22.6) | 11.70 (16.2) |
| $C_{max,ss,norm}$ (µg/mL*kg) | 836.27 (16.8) | 826.41 (20.6) | 902.36 (18.1) |
| $A_{e(0-12)}$ (mg) [a] | 82.45 [b] ±11.58 | 91.69 [c] ±30.20 | 81.59 ±18.69 |
| $t_{max}$ (h) [d] | 0.8 (0.5-4) | 0.5 (0.5-4) | 0.8 (0.5-1.5) |
| $t_{1/2}$ (h) | 15.82 (10.0) | 15.99 (8.8) | 15.97 (15.9) |

CV=coefficient of variation
Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-12)ss}$ in post-text tables and listings.
a Arithmetic mean±standard deviation
b N=8 subjects only; $A_{e(0-12)}$ was not calculated for 4 subjects due to missing urine samples (3 subjects) or incomplete urine collection (1 subject) at t=8h.

c N=11 subjects only; $A_{e(0-12)}$ was not calculated for 1 subject due to missing urine samples at t=8h.
d Median (range)

After multiple dosing with 200mg lacosamide twice daily, mean $AUC_{\tau,ss}$ of lacosamide was slightly lower in White subjects compared to Asian and Black subjects. After normalization by body weight, which was slightly higher in White subjects, no difference was observed for $AUC_{\tau,ss,norm}$ between the 3 ethnic groups. Similarly, no difference was observed for mean $C_{max,ss}$ between the 3 ethnic groups (Table 3).

**Table 3. Point estimates and 90% confidence intervals for AUC and $C_{max}$ of lacosamide.**

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

Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-12)ss}$ in post-text tables and listings.

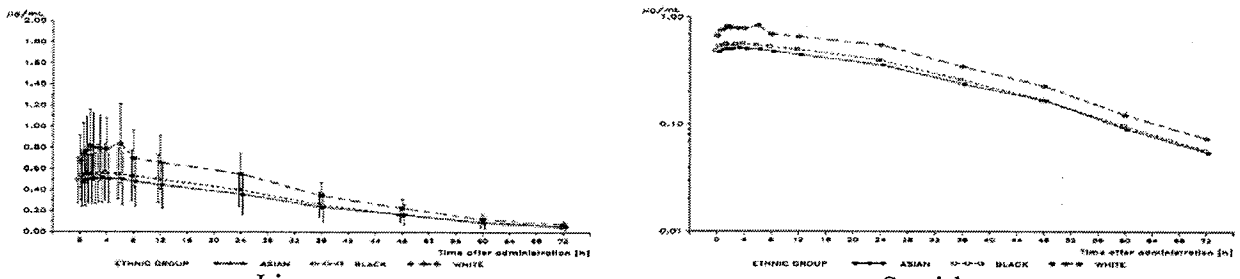
The mean cumulative amount of lacosamide excreted into urine within 12 hours after dosing ($A_{e(0-12)}$) was slightly higher in Black subjects compared to Asian and White subjects.

The mean renal clearance ($CL_R$) was slightly lower in Asian subjects (approximately 0.73L/h) compared to Black and White subjects (approximately 0.83L/h and 0.84L/h, respectively.

Mean $C_{trough}$ was slightly higher in Black and Asian subjects (approximately 6.4µg/mL and 6.5µg/mL, respectively) compared to White subjects (approximately 5.5µg/mL).

*Plasma PK Profiles for SPM 12809*

Mean plasma concentration-time curves of SPM 12809 after last dosing on Day 4 are shown in Figure 2.



Linear Semi-log

**Figure 2. Mean plasma concentrations of SPM 12809 after multiple oral administration of 200mg lacosamide at steady state (Day 4) (N=12 for each ethnic group).**

Mean plasma concentrations of SPM 12809 were lower in Asian and Black subjects compared to White subjects. The maximum mean plasma concentration was approximately 0.5µg/mL in Asian and Black subjects compared to 0.8µg/mL in White subjects. Seventy-two hours after administration of 200mg lacosamide at steady state, mean plasma concentrations were between 0.05 and 0.07µg/mL in the 3 ethnic groups (Table 4). Mean $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max}$, and $C_{max,norm}$ of metabolite SPM 12809 were approximately 30-50% lower in Asian and Black subjects compared to White subjects (Table 5). Mean $A_{e(0-12)}$ of SPM 12809 was also approximately 30-50% lower in Asian and Black subjects compared to White subjects.

Mean $C_{trough}$ of SPM 12809 was slightly lower in Asian and Black subjects compared to White subjects.

**Table 4. Pharmacokinetic parameters (geometric mean and CV [%]) of SPM 12809.**

| Parameter (unit) | Metabolite SPM 12809 | | |
|---|---|---|---|
| | Asian (N=12) | Black (N=12) | White (N=12) |
| $AUC_{\tau,ss}$ (µg/mL*h) | 5.30 (49.1) | 5.69 (62.9) | 8.35 (43.2) |
| $AUC_{\tau,ss,norm}$ (µg/mL*h*kg) | 368.6 (51.8) | 397.5 (58.5) | 643.8 (39.4) |
| $C_{max,ss}$ (µg/mL) | 0.480 (47.7) | 0.516 (62.5) | 0.814 (43.7) |
| $C_{max,ss,norm}$ (µg/mL*kg) | 33.35 (50.0) | 36.10 (58.3) | 62.73 (39.7) |
| $A_{e(0-12)}$ (mg) [a] | 17.45 [b] ±6.96 | 24.07 [c] ±11.68 | 32.76 ±13.61 |
| $t_{max}$ (h) [d] | 2.0 (0.5-4) | 2.5 (1.5-6) | 1.8 (0.5-6) |
| $t_{1/2}$ (h) | 20.261 (16.3) | 20.435 (14.5) | 20.206 (19.5) |

CV=coefficient of variation

Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-12)ss}$ in post-text tables and listings.
a Arithmetic mean±standard deviation
b N=8 subjects only; $A_{e(0-12)}$ was not calculated for 4 subjects due to missing urine samples (3 subjects) or incomplete urine collection (1 subject) at t=8h.
c N=11 subjects only; $A_{e(0-12)}$ was not calculated for 1 subject due to missing urine samples at t=8h.
d Median (range)

**Table 5. Point estimates and 90% confidence intervals for AUC and $C_{max}$ of SPM 12809.**

| Parameter | Metabolite SPM 12809 | |
|---|---|---|
| | Ratio "Asian/White" (N=12) | Ratio "Black/White" (N=12) |
| $AUC_{\tau,ss}$ | 0.6351 (0.4526, 0.8912) | 0.6809 (0.4853, 0.9555) |
| $AUC_{\tau,ss,norm}$ | 0.5725 (0.4123, 0.7949) | 0.6174 (0.4447, 0.8573) |
| $C_{max,ss}$ | 0.5898 (0.4215, 0.8253) | 0.6346 (0.4535, 0.8879) |
| $C_{max,ss,norm}$ | 0.5316 (0.3843, 0.7354) | 0.5754 (0.4160, 0.7960) |

Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-12)ss}$ in post-text tables and listings.

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

With respect to SPM 12809, mean $AUC_{\tau,ss}$, $AUC_{\tau,ss,norm}$, $C_{max,ss}$, $C_{max,ss,norm}$ as well as $A_{e(0-12)}$ of SPM 12809 were approximately 30% to 50% lower in Asian and Black subjects compared with White subjects. The data indicated the metabolism differences between races.

SPM 12809 has been shown not to be pharmacologically active and absolute differences for the plasma concentrations of SPM 12809 observed in this trial are small, especially when compared to the more than 10-fold higher plasma concentrations of the parent compound lacosamide. Because lacosamide plasma concentrations are very similar in all ethnic groups and SPM 12809 plasma concentrations are decreased in Asian and Black subjects compared to White subjects, there is no safety concern.

*4.2.4 Food Effect Study*

*4.2.4.1 Study SP600: Open-label, randomized, single dose, two-way cross-over study to evaluate the effect of food on the bioavailability of SPM 927 in 24 healthy male Caucasian volunteers*

---

**Study Type:** Single dose food effect study.

**Clinical Investigator:** [redacted] b(4)

**Objectives:** To evaluate the influence of food on the pharmacokinetics of SPM 927 when given after a high-fat breakfast or in the fasting state.

**Study Design:** This was a was a randomized, open-label, single-dose, single-center, 2-way cross-over study in healthy male subjects. Subjects received a single dose of 300 mg LCM (3 tablets containing 100mg each) under fasting conditions in 1 period and 30 minutes after a high-fat breakfast in the other period. There was a 7-day washout between treatments.

- Treatment A: 3 x 100 mg SPM 927 tablets as a single dose under fasting conditions
- Treatment B: 3 x 100 mg SPM 927 tablets as a single dose 30 minutes after start of a high-fat breakfast

**Blood sampling times:** Samples (7 ml) were obtained at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 h post dose.

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

**Analytical Methodology (Validation Report No. [redacted]a215)** b(4)
Same as Study SP587.

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

**Results:**
Study Population: 24 male Caucasian subjects were enrolled and they all completed the trial. The mean age of the subjects was 30.5 years (range, 19-39 years).

Pharmacokinetics: Mean PK profiles of SPM 927 following both treatments are shown in Figure 1. The PK results and statistical analysis for SPM 927 are summarized in Tables 1 and 2.

**Figure 1.** Mean Plasma Concentrations of SPM 927 After Oral Administration of 300 SPM mg to Healthy Volunteers Under Fed and Fasted Conditions.

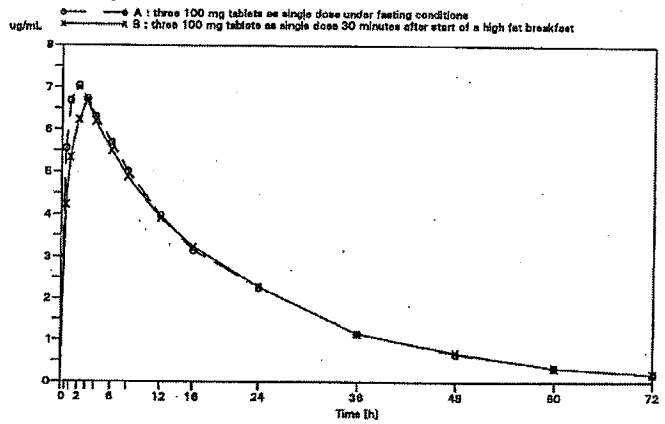





**Table 1: Mean (CV) PK parameters of SPM 927 following single-dose administration of 300mg SPM 927 in a fed or a fasted state in healthy male subjects.**

| PK Parameters | Treatment A - Fasted | Treatment B - Fed |
|---|---|---|
| $C_{max}$ (ng/mL) | 7.74 (15.6) | 7.49 (18.7) |
| $AUC_{0-t}$ (ng.hr/mL) | 142.0 (13.2) | 139.2 (13.2) |
| $AUC_{0-\infty}$ (ng.hr/mL) | 145.6 (13.4) | 143.1 (13.4) |
| Tmax (h) | 1.61 (64.7) | 2.02 (55.8) |
| T1/2 (h)[#] | 13.3 (15.1) | 13.4 (11.5) |

[#]Geometric mean (%CV)

**Table 2. Summary of the statistical comparison of PK of SPM 927 following oral administration of 300 mg to healthy volunteers under fed and fasted conditions.**

| PK Parameters[a] | Fed | Fasted | Fed : Fasted ratio | |
|---|---|---|---|---|
| | | | Point estimate | 90% Confidence Intervals |
| $C_{max}$ (ng/mL) | 7.39 | 7.65 | 0.97 | 90.3 – 103.1 |
| $AUC_{0-t}$ (ng.hr/mL) | 138.0 | 140.8 | 0.98 | 96.3 – 99.8 |
| $AUC_{0-\infty}$ (ng.hr/mL) | 141.9 | 144.3 | 0.98 | 96.5 – 100.2 |
| Tmax (h)[#] | 2.0 | 1.5 | 1.33 | 100.0 – 166.7 |

[a]Least-Squares (geometric) mean
[#]Median, Non-parametric

**Comments:** Point estimates for the ratio of PK of SPM 927 under fed to fasted state were near 1 and the 90% CIs were within the bioequivalence range of (0.8, 1.25) for AUC and Cmax. The median Tmax of SPM 927 is prolonged from 1.5 h to 2 h with co-administration a high-fat breakfast.

**Conclusion**: The results of the study demonstrate that food has no influence on the pharmacokinetics of SPM 927.

*4.2.5 In Vivo Drug Interaction Studies*

*4.2.5.1 Omeprozole— Study SP863: Open-label multiple-dose trial to evaluate the pharmacokinetic effect of lacosamide on omeprazole and vice versa in healthy male White subjects*

---

| | |
|---|---|
| **Study Period:** | August 17, 2005 to October 20, 2005 |
| **Sample Analysis Periods:** | September 29, 2005 to October 28, 2005 (plasma)<br>October 28, 2005 to November 07, 2005 (urine) |
| **Analytical Site:** | SCHWARZ BIOSCIENCES GmbH, Department of Bioanalytics, Alfred-Nobel-Straße 10, 40789 Monheim am Rhein, Germany |

| |
|---|
| **Title of trial**: Open-label multiple-dose trial to evaluate the pharmacokinetic effect of lacosamide on omeprazole and vice versa in healthy male White subjects |
| **Investigator**: [redacted] |
| **Trial site**: [redacted] |

b(4)

| | |
|---|---|
| **Publication (reference)**: None | |
| **Studied period (years)**:<br>First subject enrolled: 17 Aug 2005<br>Last subject completed: 20 Oct 2005 | **Phase of development**: Phase 1 |
| **Objectives**: The primary objectives were to evaluate the possible influence of 300mg lacosamide twice daily multiple-dose treatment on the pharmacokinetics of 40mg omeprazole single-dose treatment (Treatment A) and the possible influence of 40mg omeprazole once daily multiple-dose treatment on the pharmacokinetics of 300mg lacosamide single-dose treatment (Treatment B) in healthy male White subjects.<br>The secondary objectives were to evaluate additional pharmacokinetic (PK) parameters of lacosamide, SPM 12809, and omeprazole. In addition, safety and tolerability were evaluated. | |
| **Methodology**: This was a randomized, open-label, crossover Phase 1 trial to assess the effect of lacosamide on the pharmacokinetics of omeprazole and vice versa. All subjects received 2 treatments (A and B) in a randomized order (sequence A-B or B-A):<br>Treatment A: Subjects received single doses of omeprazole on Days 1 and 8 and in addition a 6-day multiple-dose treatment with lacosamide from Day 3 to Day 8.<br>Treatment B: Subjects received single doses of lacosamide on Days 1 and 8 and in addition a 7-day multiple-dose treatment with omeprazole from Day 3 to Day 9.<br>The total duration of the trial was approximately 8 weeks for each subject from the Eligibility Assessment (EA) to the Safety Follow-Up visit (SFU). The Treatment Phase started 2 to 14 days after EA and consisted of 2 Treatment Periods (1 and 2), separated by a Wash-Out Period of at least 7 days between the last administration of trial medication in Treatment Period 1 and the first administration of trial medication in Treatment Period 2. An SFU was performed at least 14 days after the last administration of trial medication. | |
| **Number of subjects (planned and analyzed)**: Thirty-four subjects were planned to be randomized and 34 subjects were planned to be taken into account for primary analysis. Subjects who discontinued early were replaced. Thirty-six subjects were randomized and were valid for safety analysis. Thirty-four subjects were valid for PK analysis. | |

APPEARS THIS WAY
ON ORIGINAL

**Diagnosis and main criteria for inclusion**: Healthy male White subjects aged between 18 and 45 years and with a normal body mass index (19-28kg/m$^2$) were enrolled. Subjects had to be extensive metabolizers for CYP2C19. An "extensive" metabolizer was defined as a "non-poor" metabolizer in this trial.

**Test products, doses and mode of administration, batch numbers**:

Omeprazol — 40mg gastric juice-resistant capsule, administered orally; batch numbers: 0506100002 (administered in Treatment A) and 0505310001 (administered in Treatment B)

b(4)

Two single doses of 40mg omeprazole were administered in Treatment A and multiple doses of 40mg once daily were administered in Treatment B.

Lacosamide 100mg film-coated tablet, administered orally; batch number: 0405120004

Multiple ascending doses of 100, 200, and 300mg lacosamide twice daily (200, 400, and 600mg/day) were administered in Treatment A and 2 single doses of 300mg were administered in Treatment B.

**Duration of treatment**: Subjects received 2 single-dose treatments with omeprazole and a 6-day multiple-dose treatment with lacosamide in Treatment A and 2 single-dose treatments with lacosamide and a 7-day multiple-dose treatment with omeprazole in Treatment B.

**Reference therapy, dose and mode of administration, batch number**: None

**Criteria for evaluation**:

Pharmacokinetics: The following parameters were calculated as primary PK parameters in this trial:

- $AUC_{(0-tz)}$ and $C_{max}$ of omeprazole in Treatment A
- $AUC_{(0-tz)}$ and $C_{max}$ of lacosamide in Treatment B

The following parameters were calculated as secondary PK parameters in Treatment A:

- $AUC_{(0-\infty)}$, $t_{1/2}$, $t_{max}$, and CL/f of omeprazole
- $AUC_{\tau,ss}$, $C_{max,ss}$, $t_{max,ss}$, CL/f, $C_{trough}$, and $C_{min,ss}$ of lacosamide and SPM 12809

The following parameters were calculated as secondary PK parameters in Treatment B:

- $AUC_{(0-\infty)}$, $t_{1/2}$, $t_{max}$, CL/f, $CL_R$, and $A_e$ of lacosamide and $t_{max}$ and $A_e$ of SPM 12809
- $AUC_{(0-tz)}$ and $C_{max}$ of SPM 12809

In Treatment B, further secondary parameters for SPM 12809 and omeprazole that were planned per Trial Protocol could not be calculated.

Safety: Adverse events (AEs), determination of changes in safety laboratory parameters that are relevant to safety, vital sign parameters (pulse rate, blood pressure), and electrocardiogram (ECG) parameters

**Statistical methods**: Thirty-four subjects were planned to be randomized (17 subjects per treatment sequence) and 34 subjects were planned to be taken into account for primary analysis (17 subjects per arm).

Descriptive statistics provide an overview of the PK and safety results. For categorical parameters, these consist of the number and percentage of subjects in each category. For continuous parameters, descriptive statistics include n (number of non-missing values), arithmetic mean, standard deviation, median, minimum, and maximum.

For primary analysis, $AUC_{(0-tz)}$ and $C_{max}$ of omeprazole given alone and at steady state of lacosamide and $AUC_{(0-tz)}$ and $C_{max}$ of lacosamide given alone and at steady state of omeprazole were compared by means of an analysis of variance (ANOVA). The statistical analysis was carried out with the main purpose of deriving confidence intervals for the ratio "medication given at steady state of other medication"/"medication given alone" for the primary PK parameters of lacosamide and omeprazole.

The dosing schedule for the 2 treatments is displayed below:

| | | | Administration of trial medication (Period 1 or 2) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatments | Trial medication | Dose | Day 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Treatment A | Lacosamide | 300mg bid | | | | | xx | xx | xx | xx | |
| | | 200mg bid | | | | xx | | | | | |
| | | 100mg bid | | | xx | | | | | | |
| | Omeprazole | 40mg | x | | | | | | | x | |
| Treatment B | Lacosamide | 300mg | x | | | | | | | x | |
| | Omeprazole | 40mg | | | x | x | x | x | x | x | x |

bid=bis in die (twice daily)
Dosing schedule: x=once daily (in the morning); xx=twice daily (in the morning and the evening)

Two treatment periods were separated by at least 7 days.

**Study Rationale:** In a preclinical study, the potential for metabolic drug interactions due to cytochrome P450 (CYP) inhibition was investigated using recombinant human enzymes. In this study, CYP2C19 was inhibited by lacosamide at very high concentrations (equivalent to 450µg/mL) compared with the concentrations reached in clinical trials (mean values of approximately 14.5 µg/mL after administration of 300 mg lacosamide twice daily). Since a clinically relevant drug-drug interaction cannot be completely excluded, this interaction trial was performed to assess a potential influence of lacosamide on the pharmacokinetics of a known substrate of CYP2C19 (omeprazole).

**Dose selection:** Single doses of 300 mg lacosamide (Treatment B) and up to 300 mg lacosamide twice daily (Treatment A) represent typical dosages used in clinical trials with lacosamide. In previous clinical trials, lacosamide was generally well tolerated up to single oral doses of 600 mg as well as oral doses of 300 mg administered twice daily. To ensure good tolerability of the maximum dose of lacosamide in this trial, subjects were up-titrated over 3 days to 300 mg lacosamide twice daily.

For omeprazole, the normal therapeutic dose is 20 mg once daily; the dose of 40 mg once daily in this trial represents the upper range of the therapeutic dose range (Omeprazol- ——— Summary of Product Characteristics, 2004). b(4)

**Sample Collection:**
**Lacosamide and SPM 12809:**
For the determination of lacosamide and SPM 12809 in plasma, venous blood samples (6mL each) were drawn by venous puncture or by indwelling venous catheter into lithium-heparinized tubes.
In Treatment A, blood samples for the determination of lacosamide and SPM 12809 were taken pre-dose on Day 7 and over 12 hours after the morning dose on Day 8 at the following timepoints:
• Day 7: 0 (pre-dose) and 12 hours (pre-dose),
• Day 8: 0 (pre-dose), 1, 2, 4, 8, and 12 hours (pre-dose)

In Treatment B, blood samples were taken over 48 hours after administration of trial medication on Days 1 and 8 at the following time points:
• Days 1 and 8: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours

**Omeprazole:**
For the determination of omeprazole in plasma, venous blood samples (4mL each) were drawn by venous puncture or indwelling venous catheter into lithium-heparinized tubes.
In Treatment A, blood samples for the determination of omeprazole were taken over 24 hours after administration of trial medication on Days 1 and 8 at the following time points:
• Days 1 and 8: 0 (pre-dose), 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours
In Treatment B, blood samples were taken over 4 hours after administration of trial medication on Day 8 at the following time points:
• Day 8: 0 (pre-dose), 1, 1.5, 2, and 4 hours

In Treatment A, no urine samples were collected for PK analysis.

In Treatment B, urine was collected pre-dose on Days 1 and 8 and over 48 hours post-dose on these days (collection periods: 0-6, 6-12, 12-24, and 24-48 hours) for the determination of urine concentrations of lacosamide and SPM 12809.

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method (Validation Report No.ikp094/04-05-he). The LOQ for LCM in plasma was 0.1 µg/mL and in urine was 5.29 µg/mL. The LOQ for SPM 12809 in plasma was 0.02 µg/mL and in urine was 1.14 µg/mL. See tables below for summary of analytical assay data.

| Analyte | Calibrated range | Defined LLOQ | Precison (%) for QCs | Accuracy (%) for QCs |
|---|---|---|---|---|
| SPM 927 in human plasma | 105.50 – 20021.86 µg/L | 105.50 µg/L | Better than 10 % | Better than -8 % |
| Desmethyl-SPM 927 in human plasma | 22.13 – 4200.00 µg/L | 22.13 µg/L | Better than 10 % | Better than -3 % |
| SPM 927 in human urine | 5.440 – 499.775 µg/mL | 5.440 µg/mL | Better than 8 % | Better than 5 % |
| Desmethyl-SPM 927 in human urine | 1.161 – 106.660 µg/mL | 1.161 µg/mL | Better than 11 % | Better than -6 % |
| Omeprazole in human plasma | 19.690 – 9901.470 µg/L | 19.690 µg/L | Better than 30 % | Better than 7 % |

**Subjects:** Healthy young male White subjects known to be extensive (ie, "non-poor") metabolizers for CYP2C19 were enrolled in this trial. The genotyping had been done previously by PPN to characterize subjects for the volunteer panel. No genotyping was done for this trial.

Initially, 34 subjects were enrolled. Two subjects prematurely discontinued the trial and were replaced. In total, 36 subjects were randomized and treated in this trial and 34 subjects completed the trial and included in PK analysis.

Subject 80011 (A-B) was withdrawn from the trial on Day 7 of Treatment A due to an AE and Subject 80019 (B-A) withdrew his consent on Day 3 of Treatment B. The 2 subjects were replaced with Subjects 81011 and 81019.

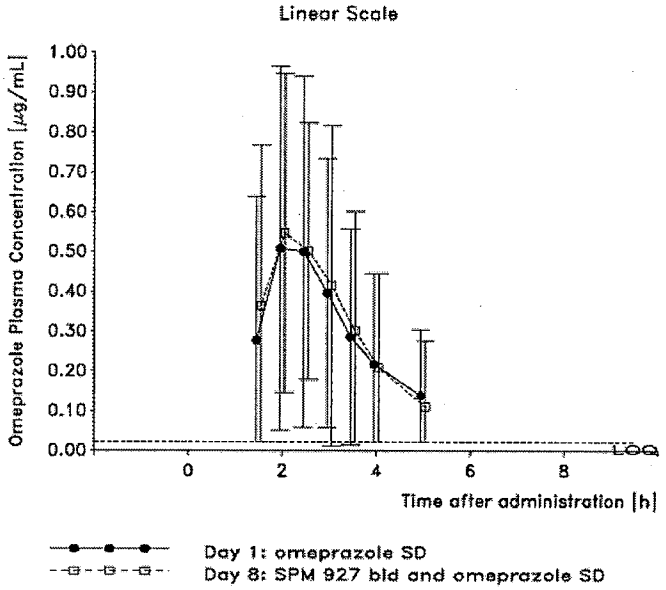
**Table 1. Demographic Data-Safety Set.**

| Parameter (unit) | Sequence A-B (N=18) | Sequence B-A (N=18) | Total (N=36) |
|---|---|---|---|
| | Mean ± standard deviation (range) | | |
| Age (years) | 34.8±7.2 (19-45) | 37.3±6.6 (21-43) | 36.0±6.9 (19-45) |
| Body height (m) | 1.807±0.06 (1.70-1.88) | 1.784±0.06 (1.70-1.92) | 1.796±0.06 (1.70-1.92) |
| Body weight (kg) | 79.10±8.20 (65.0-99.1) | 78.08±7.90 (66.5-95.6) | 78.59±7.95 (65.0-99.1) |
| Body mass index ($kg/m^2$) | 24.22±2.19 (20.8-28.0) | 24.54±2.40 (20.2-27.9) | 24.38±2.27 (20.2-28.0) |

Treatment key: Treatment A: omeprazole single-dose with and without lacosamide at steady state; Treatment B: lacosamide single-dose with and without omeprazole at steady state

**Pharmacokinetic Results:**

*Effect of multiple dose lacosamide on single-dose omeprazole PK:*




bid=bis in die (twice daily); LOQ=lower limit of quantification (0.02µg/mL); PKS=Pharmacokinetic Set; SD=single dose; SPM 927=lacosamide

**Figure 1. Mean plasma concentrations of omeprazole after administration alone and at steady state of lacosamide – PKS (N=34)**

**Table 2. Pharmacokinetic parameters of omeprazole after administration of a single dose of 40 mg omeprazole alone and at steady state of lacosamide.**

| Parameter (unit) | Statistic | Omeprazole (N=34) | Lacosamide + omeprazole (N=34) |
|---|---|---|---|
| $AUC_{(0-tz)}$ (µg/mL*h) | Geometric mean (CV %) | 1.027 (102.7) | 1.127 (83.1) |
| $C_{max}$ (µg/mL) | | 0.5857 (71.4) | 0.6471 (61.1) |
| $AUC_{(0-\infty)}$ (µg/mL*h) | | 1.182 (87.5)[a] | 1.340 (70.6)[a] |
| $t_{1/2}$ (h) | | 0.867 (31.7)[a] | 0.851 (34.7)[a] |
| CL/f (L/h) | | 33.85 (87.5)[a] | 29.85 (70.6)[a] |
| $t_{max}$ (h) | Median (range) | 2.00 (1.0-5.0) | 2.00 (1.25-5.0) |

CV=coefficient of variation

[a] Note that for 4 subjects $AUC_{(0-\infty)}$, $t_{1/2}$, and CL/f could not be calculated (N=30).

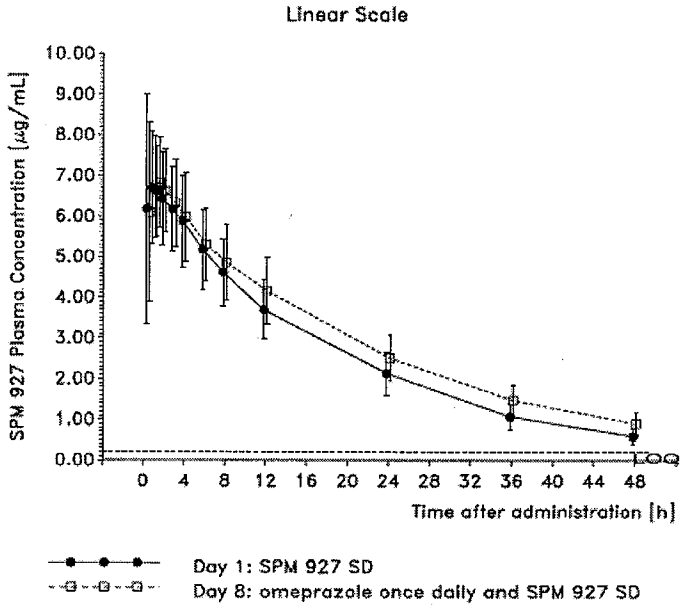
The ratios and 90% CIs for the comparison "omeprazole+lacosamide (test) / omeprazole alone (reference)" for $AUC_{(0-tz)}$ and $C_{max}$ of omeprazole are presented in the following table.

**Table 3. Summary of analysis of variance for primary PK parameters of omeprazole - PKS**

| Parameter | Ratio | Estimate | 90% confidence interval |
|---|---|---|---|
| $AUC_{(0\text{-}tz)}$ | omeprazole+lacosamide / omeprazole alone | 1.0976 | (0.9963, 1.2092) |
| $C_{max}$ | | 1.1049 | (0.9793, 1.2466) |

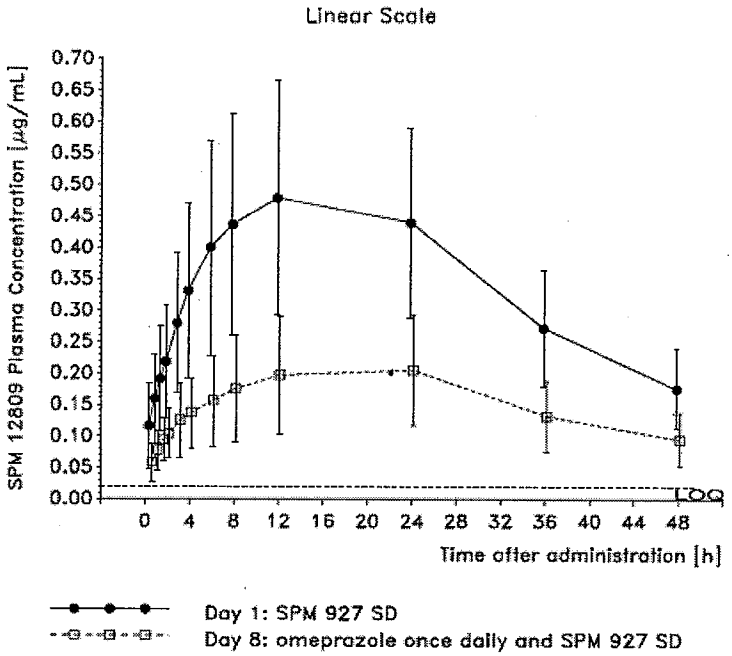
*Effect of multiple dose omeprazole on single dose lacosamide and SPM 12809 PK:*
The mean plasma concentration-time curves of lacosamide and SPM 12809 after single-dose administration of lacosamide on Day 1 and Day 8 (linear scale) are shown in Figures 2 and 3, respectively. PK parameters are summarized in Table 4. The ratios and 90% CIs for the comparison "lacosamide+omeprazole (test) / lacosamide alone (reference)" for $AUC_{(0\text{-}tz)}$ and $C_{max}$ of lacosamide are presented in Table 5.

The administration of 40 mg omeprazole once daily multiple-dose treatment did not influence the pharmacokinetics of 300 mg LCM single-dose treatment but reduced the formation of SPM 12809 by approximately 60%. This indicates that CYP2C19 is responsible for the formation of SPM 12809. The findings are similar to what was found in Study 643 (CYP2C19 EM and PM study).




LOQ=lower limit of quantification (0.11µg/mL); PKS=Pharmacokinetic Set; SD=single dose; SPM 927=lacosamide

**Figure 2. Mean plasma concentrations of lacosamide after administration alone and following multiple doses of omeprazole – PKS (N=34)**




LOQ=lower limit of quantification (1.16µg/mL); PKS=Pharmacokinetic Set; SD=single dose; SPM 927=lacosamide

**Figure 3. Mean plasma concentrations of SPM 12809 after administration of lacosamide alone and following multiple doses of omeprazole – PKS (N=34)**

**Table 4. Pharmacokinetic parameters of lacosamide and SPM 12809 after administration of a single dose of 300mg lacosamide alone and following multiple doses of omeprazole – PKS.**

| Parameter (unit) | Statistic | Lacosamide | | SPM 12809 | |
|---|---|---|---|---|---|
| | | Lacosamide (N=34) | Omeprazole + lacosamide (N=34) | Lacosamide (N=34) | Omeprazole + lacosamide (N=34) |
| $AUC_{(0\text{-}tz)}$ (µg/mL*h) | Geometric mean (CV %) | 122.9 (20.5) | 139.3 (20.1) | 15.57 (41.5) | 6.901 (45.5) |
| $C_{max}$ (µg/mL) | | 7.366 (19.8) | 7.335 (16.9) | 0.4588 (44.4) | 0.1940 (47.8) |
| $AUC_{(0\text{-}\infty)}$ (µg/mL*h) | | 134.0 (22.1) | 160.3 (22.4) | n.d. [a] | n.d. [a] |
| $t_{1/2}$ (h) | | 13.19 (12.7) | 16.23 (13.5) | n.d. [a] | n.d. [a] |
| CL/f (L/h) | | 2.238 (22.1) | 1.872 (22.4) | n.d. [a] | n.d. [a] |
| $CL_R$ (L/h) | | 0.5950 (29.9) | 0.5790 (29.0) | n.d. [a] | n.d. [a] |
| $t_{max}$ (h) | Median (range) | 1.00 (0.5-3.0) | 1.00 (0.5-3.0) | 12.00 (6.0-24.0) | 24.00 (8.0-36.0) |
| $A_e$ (mg) | Arithmetic mean ± SD | 82.67±21.56 | 95.88±23.36 | 51.34±19.89 | 21.78±8.80 |

a Since the sampling time was not long enough to determine $t_{1/2}$ of SPM 12809, $AUC_{(0-\infty)}$, CL/f, and $CL_R$ of SPM 12809 could also not be calculated.
CV=coefficient of variation; SD=standard deviation; PKS=Pharmacokinetic Set

**Table 5. Summary of analysis of variance for primary PK parameters of lacosamide – PKS.**

| Parameter | Ratio | Estimate | 90% confidence interval |
|---|---|---|---|
| $AUC_{(0-tz)}$ | lacosamide+omeprazole / lacosamide alone | 1.1330 | (1.1015, 1.1654) |
| $C_{max}$ | | 0.9958 | (0.9474, 1.0467) |

**Safety Results:** No death or serious AE occurred in this trial. The most frequently reported TEAEs were dizziness, oral paraesthesia, headache, and fatigue.

One subject experienced an AE of "electrocardiogram T wave inversion" which was reported as an AE of special interest and led to the withdrawal of the subject from the trial. The T wave inversion was not accompanied by clinical symptoms. Two subjects experienced AEs of "rash" which was defined as a significant AE.

**Conclusions:**

- Co-administration of multiple doses of lacosamide did not alter the rate and extent of absorption of the CYP2C19 substrate omeprazole, indicating that lacosamide does not inhibit CYP2C19.

- Co-administration of the CYP2C19 inhibitor omeprazole did not alter the rate and extent of absorption of lacosamide.

- However, Co-administration of the CYP2C19 inhibitor omeprazole had a clear influence on the pharmacokinetics of the main metabolite of lacosamide, SPM 12809. Exposure (measured as $AUC_{(0-tz)}$), $C_{max}$, and the cumulative amount of SPM 12809 excreted into urine within 48 hours after dosing ($A_e$) were reduced by approximately 55-60% and the median $t_{max}$ was prolonged from 12 to 24 hours when lacosamide was administered after multiple doses of omeprazole compared with administration alone. This indicates that CYP2C19 is mainly responsible for the formation of SPM 12809. These results are in accordance with the results from a previous study in poor and extensive metabolizers for CYP2C19 (SP643). In SP643, the pharmacokinetics of lacosamide were similar in poor and extensive metabolizers while $AUC_{(0-tz)}$, $C_{max}$, and the amount excreted into urine of SPM 12809 were reduced by approximately 70% in poor metabolizers. The results from both studies indicate that CYP2C19 is responsible for the formation of SPM 12809.

*4.2.5.2 Digoxin—Study SP644: Double-blind, placebo-controlled, randomized crossover Phase 1 trial to investigate a possible influence of SPM 927 on the steady state pharmacokinetics, pharmacodynamics, safety and tolerability of digoxin in healthy male Caucasian subjects*

---

**Study Period:** October 27, 2003 to January 5, 2004
**Sample Analysis Periods:** January 27, 2005 to February 10, 2005 (plasma)
January 14, 2005 to Juanry 15, 2005 (urine)
**Analytical Site:** SCHWARZ BIOSCIENCES GmbH, Department of Bioanalytics, Alfred-Nobel-Straße 10, 40789 Monheim am Rhein, Germany

| | |
|---|---|
| **Title of trial**: Double-blind, placebo-controlled, randomized crossover Phase 1 trial to investigate a possible influence of SPM 927 on the steady state pharmacokinetics, pharmacodynamics, safety and tolerability of digoxin in healthy male Caucasian subjects | |
| **Investigator**: [redacted] b(4) | |
| **Trial site**: [redacted] | |
| **Publication (reference)**: None | |
| **Studied period (years)**: -<br>**First subject enrolled**: 27 Oct 2003<br>**Last subject completed**: 05 Jan 2004 | **Phase of development**: Phase 1 |
| **Objectives**: The primary objective of this trial was to evaluate the pharmacokinetics of digoxin with and without co-administration of lacosamide (SPM 927).<br>The secondary objectives were the pharmacodynamics, safety, and tolerability of digoxin with and without co-administration of lacosamide.<br>The influence of digoxin on the pharmacokinetics of lacosamide was also assessed in a "historical comparison" with data for lacosamide from previous trials. | |
| **Methodology**: This was a double-blind, placebo-controlled, multiple-dose, 2-way crossover trial with a 7-day digoxin Run-In Phase followed by the following 2 treatments in a randomized order:<br>Treatment A (test): 0.25mg digoxin once daily plus 200mg lacosamide twice daily over 3.5 days<br>Treatment B (reference): 0.25mg digoxin once daily plus placebo (matched to lacosamide) twice daily over 3.5 days<br>Digoxin treatment was continued in a 6-day Wash-Out Phase between the 2 treatments. | |
| **Number of subjects (planned and analyzed)**: Approximately 20 subjects were planned to be randomized. Twenty-three subjects were randomized; 20 subjects were treated and analyzed. | |
| **Diagnosis and main criteria for inclusion**: Subjects included in the trial were healthy, 26- to 44-year-old White males. | |

**Test product, dose and mode of administration, batch number:**

0.25mg digoxin tablets [redacted] manufactured by [redacted] and supplied by SCHWARZ BIOSCIENCES GmbH, Monheim, Germany; batch number: WE12795

b(4)

Dose: 0.25mg digoxin orally once daily after an initial dosing 3 times daily on Day 1

100mg lacosamide film-coated tablets, manufactured by SCHWARZ BIOSCIENCES GmbH, Monheim, Germany; batch number: 228920

Dose: 2 tablets of 100mg lacosamide orally twice daily

**Duration of treatment**: 21 days with digoxin treatment, including 3.5 days of co-administration with lacosamide

**Reference therapy, dose and mode of administration, batch number:**

Placebo film-coated tablets matched to lacosamide, manufactured by SCHWARZ BIOSCIENCES GmbH, Monheim, Germany; batch number: 228850

**Criteria for evaluation:**

**Pharmacokinetics**: Primary pharmacokinetic (PK) parameters of digoxin were $AUC_{(0\text{-}24)ss}$ and $C_{max,ss}$, as well as the ratio "Treatment A/Treatment B" of the parameters. Secondary PK parameters of digoxin were $t_{max,ss}$, $C_{min,ss}$, PTF (%), and $C_{trough}$. Further PK parameters were $AUC_{(0\text{-}12)ss}$, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, and $A_{e(0\text{-}12)ss}$ of lacosamide and SPM 12809 and $A_{e(0\text{-}24)ss}$ of digoxin.

**Pharmacodynamics**: Electrocardiogram (ECG) parameters on Day 8 (predose) were compared with ECG parameters during Treatments A and B (1 hour after dosing on Days 11 and 21).

**Safety**: To assess the safety and tolerability of digoxin with or without co-administration of lacosamide, adverse events (AEs), safety laboratory parameters, ECG parameters, vital signs, and physical findings were evaluated.

**Statistical methods**: Descriptive statistics were displayed to provide an overview of PK, pharmacodynamic, and safety results.

The logarithms of $AUC_{(0\text{-}24)ss}$ and $C_{max,ss}$ were analyzed using an analysis of variance (ANOVA) including fixed factors for "treatment," "period," and "treatment sequence" and a random factor for "subject within treatment sequence." Point estimates (LS-Means) and 90% confidence intervals (CIs) for the ratio "Treatment A / Treatment B" were calculated by retransformation of the logarithmic data using the root mean square of error of the ANOVA. The absence of interaction was concluded if the 90% CI was fully contained in the equivalence range of (0.80, 1.25) for both parameters.

All subjects received 2 treatments (A and B) in randomized order in a crossover design:

| Run-In (digoxin) Days 1-7 | → | Treatment 1 (A or B) Days 8-11 | → | Wash-Out (digoxin) Days 12-17 | → | Treatment 2 (B or A) Days 18-21 | → | Wash-Out Days 22-24 |
|---|---|---|---|---|---|---|---|---|

*Reviewer's Note:* *In vitro study with Caco-2 cells suggested that lacosamide is not a P-gp inhibitor.*

**Dose selection:** The proposed therapeutic doses are 50 — mg twice daily. The chosen dosage of 200 mg lacosamide administered twice daily represents a clinically relevant dose. b(4)

The 0.25 mg dose of digoxin administered once daily represents a dose normally used in clinical practice, and the 200mg dose of lacosamide administered twice daily is considered a clinically relevant dose. —— (digoxin) was chosen as reference as it has been used as reference in several previous interaction studies with digoxin preparations. b(4)

**Sample Collection:**
The pharmacokinetics of lacosamide were assessed under steady-state conditions on Days 11 and 21 over the dosing interval of 12 hours. Trough levels (before the morning and the evening dose) were measured on Days 10 and 20.

Venous blood samples were drawn by venous puncture or by an indwelling venous catheter into lithium-heparinized tubes to determine plasma concentrations of lacosamide and SPM 12809 at the following time points:
• Pre-administration on Day 1 (blank), pre-morning and pre-evening dose on Days 10 and 20 (trough levels) and on Days 11 and 21 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the last administration (in total: 25 plasma samples of 6mL)

The pharmacokinetics of digoxin were assessed under steady-state conditions on Days 11 and 21 over the dosing interval of 24 hours. Trough levels were measured on Days 8, 10, 18, and 20.

Venous blood samples were drawn by venous puncture or by an indwelling venous catheter to determine serum concentrations of digoxin at the following time points:
• Pre-administration on Day 1 (blank), pre-morning dose on Days 8, 10, 18, and 20 and on Days 11 and 21 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after the morning dose (in total: 27 serum samples of 6mL each)

Urine was collected on Day 1 prior to dosing (blank) and on Days 11 and 21 in the intervals 0-12 and 12-24 hours after drug administration. On Days 11 and 21, 10mL aliquots of urine were taken from both collection periods for the determination of renal excretion of digoxin, lacosamide, and SPM 12809.

**Sample Analysis:** Safety digoxin serum samples were measured by the central laboratory and PK samples (serum digoxin and plasma lacosamide) by the bioanalytical laboratories.
Digoxin concentrations were determined twice in serum by radioimmunoassays with lower limits of quantification (LOQs) of 0.5ng/mL and 0.125ng/mL.

The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method in plasma (Validation Report No.ba583-03 and 613-02) and urine (Validation Report No. 585-02). The

LOQ for LCM in plasma was 0.01 µg/mL and in urine was 0.2 µg/mL. The LOQ for SPM 12809 in plasma was 0.01 µg/mL and in urine was 0.2 µg/mL.

**PD:** For the pharmacodynamic evaluation, tables displaying ECG parameters on Day 8 and Day 11/21 separated by treatment and the change from Day 8 to Day 11/21 were provided.

**Subjects:** Twenty-three subjects were enrolled in this trial and were randomized to treatment sequence A-B or B-A. Only healthy male White subjects were enrolled in the study. Of these 23 subjects, 20 subjects were treated and completed the trial; 3 subjects were not treated. Subjects 80002, 80010, and 80018 were randomized but did not receive treatment because they were withdrawn from the trial early due to Baseline condition.

**Table 1. Demographic Data.**

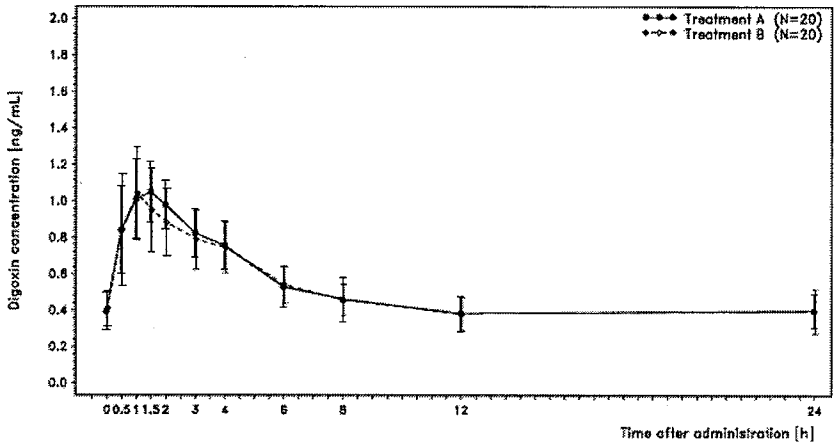
| Parameter (Unit) | Treatment sequence A-B (N=10) | Treatment sequence B-A (N=10) | Total (N=20) |
|---|---|---|---|
| | Mean ± SD (range) | | |
| Age (years) | 36.6±6.0 (26-43) | 36.9±4.9 (29-44) | 36.8±5.4 (26-44) |
| Weight (kg) | 84.9±6.2 (75-94) | 80.7±7.6 (69-94) | 82.8±7.1 (69-94) |
| Height (cm) | 181.2±5.5 (171-190) | 178.5±4.4 (170-186) | 179.9±5.1 (170-190) |
| BMI ($kg/m^2$) | 25.851±1.375 (23.15-27.77) | 25.309±1.947 (21.74-27.76) | 25.580±1.664 (21.74-27.77) |

Treatment key: Treatment A = digoxin + lacosamide; Treatment B = digoxin + placebo
BMI=body mass index; SD=standard deviation

**Pharmacokinetic Results:**

*Effect of lacosamide on digoxin steady-state PK:*
Mean plasma concentration-time curves of digoxin at steady-state in the presence and absence of lacosamide are shown in Figure 1. PK parameters of digoxin are shown in Table 2.

APPEARS THIS WAY
ON ORIGINAL




Treatment key: Treatment A = digoxin + lacosamide; Treatment B = digoxin + placebo
PKS=Pharmacokinetic Set

**Figure 1. Mean serum concentrations of digoxin at steady state (Day 11/21) with and without co-administration of lacosamide (linear scale).**

**Table 2. Pharmacokinetic parameters of digoxin at steady state (Day 11/21) with and without co-administration of lacosamide.**

| Parameter (unit) | Treatment A: Digoxin + lacosamide (N=20) | Treatment B: Digoxin + placebo (N=20) |
|---|---|---|
| | Geometric mean (CV %) | |
| $AUC_{(0\text{-}24)ss}$ (ng/mL*h) | 11.96 (18.1) | 11.68 (22.2) |
| $C_{max,ss}$ (ng/mL) | 1.12 (14.8) | 1.07 (23.8) |
| $C_{min,ss}$ (ng/mL) | 0.34 (28.8) | 0.33 (31.5) |
| $C_{trough}$ (ng/mL) | 0.39 (23.7) | 0.38 (33.7) |
| $t_{max,ss}$ (h) [a] | 1.50 (0.5-3.0) | 1.00 (0.5-3.0) |
| PTF (%) | 152.6 (29.3) | 145.9 (34.3) |
| $A_{e(0\text{-}24)ss}$ (mg) [b] | 0.091±0.0223 | 0.092±0.0287 |

CV=coefficient of variation; PKS=Pharmacokinetic Set; PTF=peak trough fluctuation
[a] Median (range)
[b] Arithmetic mean±standard deviation

Point estimates and 90% CIs for the ratio "Treatment A / Treatment B" were calculated for the primary PK parameters by retransforming the logarithmic data using the root mean square of error of the ANOVA. The ratios and 90% CIs for the primary PK parameters $AUC_{(0\text{-}24)ss}$ and $C_{max,ss}$ of digoxin are presented in Table 3.

**Table 3. ANOVA results for the ratio "Treatment A / Treatment B" for digoxin.**

| Parameter | Point estimate | 90% confidence interval |
|---|---|---|
| $AUC_{(0-24)ss}$ | 1.0241 | (0.9792, 1.0709) |
| $C_{max,ss}$ | 1.0487 | (0.9592, 1.1465) |

ANOVA=analysis of variance;
Treatment key: Treatment A = digoxin + lacosamide; Treatment B = digoxin + placebo

The pharmacokinetics of digoxin were not influenced when lacosamide was administered in combination with digoxin.

*Effect of digoxin on lacosamide:*
The influence of digoxin on the pharmacokinetics of lacosamide was assessed based on a historical comparison with data from previous trials.

**Table 4. Pharmacokinetic parameters of lacosamide with and without co-administration of digoxin at steady state ("historical comparison").**

| Parameter (unit) | SP644 | SP660 [a] | SP661 [b] | SP602 [c] |
|---|---|---|---|---|
| | Treatment A: Digoxin + lacosamide | Lacosamide alone | | |
| | N=20 | N=8 | N=12 | N=8 |
| $AUC_{(0-12)ss}$ (µg/mL*h) | 82.50 (13.6) | 68.87 (23.27) | 94.95 (17.3) | 79.05 ±1.18 [d] |
| $C_{max,ss}$ (µg/mL) | 9.46 (11.4) | 8.60 (20.14) | 11.70 (16.2) | 9.10 ±1.16 [d] |
| $C_{min,ss}$ (µg/mL) | 4.869 (17.9) | 3.819 (33.05) | 5.369 (21.1) | n.d. |
| $t_{max,ss}$ (h) | 0.75 (0.50-3.0) | 0.5 (0.5-1.5) | 0.8 (0.5-1.5) | 0.5 (0.5-1.0) |
| $A_{e(0-12)ss}$ (mg) | 58.85 ±16.12 | 83.63 ±22.01 | 81.59 ±18.69 | n.d. |

Note: Geometric mean and coefficient of variation (%) are shown for $AUC_{(0-12)ss}$, $C_{max,ss}$, and $C_{min,ss}$; median (range) is shown for $t_{max,ss}$; arithmetic mean±standard deviation is shown for $A_{e(0-12)ss}$.
n.d.=not determined; PKS=Pharmacokinetic Set
[a] SP660: Data from Group 1 (Day 6) are shown.
[b] SP661: Data from the group of White subjects are shown.
[c] SP602: Data from Group 2 are shown.
[d] Standard deviation of geometric mean is shown because coefficient of variation (%) was not determined.

Overall, PK parameters $AUC_{(0-12)ss}$ and $C_{max,ss}$ as well as $t_{max,ss}$ of lacosamide at steady state under co-administration of digoxin in the current trial (SP644) were comparable to PK parameters at steady state from previous trials where lacosamide was administered alone (SP660, SP661, and SP602). A reduction was observed with regard to the amount of lacosamide excreted into urine within a dosing interval at steady state ($A_{e(0-12)ss}$) under co-administration with digoxin compared with administration of lacosamide alone: mean $A_{e(0-12)ss}$ after administration of lacosamide alone in SP660 and SP661 corresponds to approximately 40% of the administered dose whereas mean $A_{e(0-12)ss}$ after administration of lacosamide with co-administration of digoxin in the current trial corresponds to approximately 30% of the administered dose.

**Table 5. Pharmacokinetic parameters of SPM 12809 with and without co-administration of digoxin at steady state ("historical comparison").**

| | SP644 | SP660 [a] | SP661 [b] |
|---|---|---|---|
| **Parameter (unit)** | **Treatment A: Digoxin + lacosamide** | **Lacosamide alone** | |
| | **N=20** | **N=8** | **N=12** |
| $AUC_{(0-12)ss}$ (µg/mL*h) | 11.14 (30.0) | 11.26 (47.65) | 8.35 (43.2) |
| $C_{max,ss}$ (µg/mL) | 1.02 (29.9) | 1.00 (49.28) | 0.81 (43.7) |
| $C_{min,ss}$ (µg/mL) | 0.83 (30.4) | 0.85 (45.70) | 0.60 (39.6) |
| $t_{max,ss}$ (h) | 3.00 (0.5-12.0) | 3.5 (0.5-8) | 1.8 (0.5-6) |
| $A_{e(0-12)ss}$ (mg) | 40.03±16.24 | 55.72±24.35 | 32.76±13.61 |

Note: Geometric mean and coefficient of variation (%) are shown for $AUC_{(0-12)ss}$, $C_{max,ss}$, and $C_{min,ss}$; median (range) is shown for $t_{max,ss}$; arithmetic mean±standard deviation is shown for $A_{e(0-12)ss}$.
PKS=Pharmacokinetic Set
[a] SP660: Data from Group 1 (Day 6) are shown.
[b] SP661: Data from the group of White subjects are shown.

**Pharmacodynamic Results:**

*Effect of lacosamide on PD of digoxin:*
Predose ECG parameters on Day 8 (after subjects had been treated with digoxin for 8 days) were compared with ECG parameters 1 hour after dosing in Treatment A (digoxin + lacosamide) and Treatment B (digoxin + placebo) (Day 11 or 21, depending on the treatment sequence).

Mean ECG parameters on Day 11/21 and changes from predose values on Day 8 are shown in Table 6.

**Table 6. Electrocardiogram parameters after digoxin treatment with and without co-administration of lacosamide at steady state and change from Baseline.**

| Parameter (unit) | Baseline (Day 8/ predose) | Treatment A: Digoxin + lacosamide (N=20) | | Treatment B: Digoxin + placebo (N=20) | |
|---|---|---|---|---|---|
| | | Mean value Day 11/21 +1h | Mean change from Baseline | Mean value Day 11/21 +1h | Mean change from Baseline |
| Heart rate (bpm) | 60.4 | 59.6 | -0.8 | 59.4 | -1.0 |
| RR interval (ms) | 1009.8 | 1021.8 | 12.0 | 1033.6 | 23.8 |
| PQ/PR interval (ms) | 166.8 | 178.5 | 11.7 | 170.4 | 3.6 |
| QRS duration (ms) | 87.5 | 89.6 | 2.1 | 89.3 | 1.8 |
| QT interval (ms) | 364.0 | 359.4 | -4.6 | 363.4 | -0.6 |
| QTcB interval (ms) | 363.15 | 355.90 | -7.25 | 358.30 | -4.85 |
| QTcF interval (ms) | 363.22 | 357.26 | -5.95 | 360.09 | -3.13 |
| QTcFr interval (ms) | 363.95 | 359.40 | -4.55 | 363.39 | -0.55 |

Note: Baseline is the median of the 3 predose measurements on Day 8.

*Reviewer's Comment: Due to lack of lacosamide alone arm in this study, it is not possible to determine the lacosamide's contribution to the observed change in PD.*

**Safety Results:** The incidence of AEs was higher when digoxin was administered with lacosamide compared with administration of digoxin with placebo (51 TEAEs reported by 16 subjects [80%] during Treatment A compared with 21 TEAEs reported by 8 subjects [40%] during Treatment B). No TEAE was reported during the digoxin Run-In Phase. The most common TEAEs in this trial were paresthesia and dizziness.

**Conclusions:**

- The pharmacokinetics of digoxin were not influenced by co-administration of lacosamide.
- Pharmacodynamic evaluation showed a mild prolongation of the PQ/PR interval which was more pronounced under co-administration of digoxin and lacosamide compared with administration of digoxin alone. Due to lack of lacosamide alone arm in this study, it is not possible to determine the lacosamide's contribution to the observed change in PD.
- Based on a historical comparison with PK data of lacosamide from previous trials, co-administration of digoxin had no clinically relevant influence on the pharmacokinetics of lacosamide and its main metabolite SPM 12809.

*4.2.5.3 Metformin—Study SP660: Randomized, open-label, single- and multiple-dose trial to evaluate the pharmacokinetic effect as well as safety and tolerability of SPM 927 on metformin and vice versa in healthy male Caucasian subjects*

---

**Study Period:** June 2, 2004 to August 2, 2004
**Sample Analysis Period:** June 28, 2004 and July 22, 2004 (plasma)
July 12, 2004 to July 20, 2004 (urine)
**Analytical Sites:** CHWARZ BIOSCIENCES GmbH, Department of Bioanalytics, Alfred-Nobel-Straße 10, 40789 Monheim am Rhein, Germany

| | |
|---|---|
| **Title of trial**: Randomized, open-label, single- and multiple-dose trial to evaluate the pharmacokinetic effect as well as safety and tolerability of SPM 927 on metformin and vice versa in healthy male Caucasian subjects | |
| **Investigator** [redacted] | b(4) |
| **Trial site**: [redacted] | |
| **Publication (reference)**: None | |
| **Studied period (years)**: -<br>**First subject enrolled**: 02 Jun 2004<br>**Last subject completed**: 02 Aug 2004 | **Phase of development**: Phase 1 |
| **Objectives**: Primary objective of this trial was to evaluate the possible influence of the concomitant administration of 200mg lacosamide (SPM 927) twice daily on the pharmacokinetics of 500mg metformin 3 times daily and vice versa. Furthermore, single-dose pharmacokinetics were evaluated for lacosamide (Group 1) and metformin (Group 2).<br>Secondary objective was to evaluate the possible influence of a concomitant administration of 200mg lacosamide twice daily multiple-dose treatment on the safety and tolerability of 500mg metformin 3 times daily multiple-dose treatment and vice versa. Furthermore, safety and tolerability were evaluated for lacosamide (Group 1) and metformin (Group 2) after single-dose treatment. | |
| **Methodology**: This was a randomized, open-label, parallel-group trial exploring the pharmacokinetics, safety, and tolerability of orally administered lacosamide in combination with orally administered metformin in healthy young subjects. From Eligibility Assessment 2 to 14 days before first administration of trial medication to Safety Follow-Up Visit at least 14 days after last administration of trial medication, the total duration of the trial was approximately 4 to 5 weeks for each subject including 14 treatment days. | |
| **Number of subjects (planned and analyzed)**: Sixteen subjects were enrolled with 8 subjects in each of 2 groups. All subjects completed the trial and were valid for pharmacokinetic (PK) and safety analyses. | |
| **Diagnosis and main criteria for inclusion**: Subjects were 18- to 45-year-old healthy male Whites with a body mass index between 19 and 30kg/m$^2$. | |

| |
|---|
| **Test product, dose and mode of administration, batch number**:<br>100mg lacosamide film-coated tablet, 2 tablets administered orally twice daily; batch number of bulk product: 231120<br>500mg metformin film-coated tablet [redacted] manufactured by [redacted], administered orally 3 times daily; batch number of bulk product: 0404220002 |
| **Duration of treatment**: Single-dose treatment with lacosamide (Group 1) or metformin (Group 2) followed by 12 days of multiple-dose treatment with lacosamide and/or metformin in both groups (7.5 days exposure for each drug with 3.5 days of combined treatment) |
| **Reference therapy, dose and mode of administration, batch number**: Not applicable |
| **Criteria for evaluation**:<br>**Pharmacokinetics**:<br>Primary PK parameters:<br>• $AUC_{\tau,ss}$, $C_{max,ss}$, $t_{max,ss}$, and $A_e$ of lacosamide and metformin<br>Secondary PK parameters:<br>• $AUC_{\tau,ss}$, $C_{max,ss}$, $t_{max,ss}$, and $A_e$ of the main metabolite of lacosamide, SPM 12809<br>• $t_{1/2}$, CL/f, $CL_R$, $C_{trough}$, and $C_{min,ss}$ of lacosamide, SPM 12809, and metformin<br>• $AUC_{(0-\infty)}$, $AUC_{(0-tz)}$, $C_{max}$, and $t_{max}$ of lacosamide (Day 1, Group 1), of metformin (Day 1, Group 2) and of lacosamide and SPM 12809 in saliva (Day 1, Group 1)<br>**Safety**:<br>• Tolerability, adverse events (AEs)<br>• Determination of changes in laboratory parameters relevant to safety<br>• Vital parameters (pulse rate, blood pressure, electrocardiogram [ECG]) |

| |
|---|
| **Statistical methods**: Descriptive statistics provide an overview of PK and safety results: the numbers and percentages of subjects in each category are given for categorical parameters, and n (number of non-missing values), arithmetic mean, standard deviation (SD), minimum, median, and maximum value for continuous parameters.<br>For primary analysis, PK characteristics were summarized by group for each treatment by arithmetic mean, SD, and coefficient of variation, geometric mean, geometric SD (re-transformed SD of logarithms), and coefficient of variation (CV), minimum, median, and maximum value, and the number of measurements for geometric mean for each group. Additionally, descriptive statistics as mentioned above were performed by treatment (both groups pooled).<br>The statistical analysis of secondary PK parameters ($t_{max}$ excluded) was performed using the above mentioned descriptive statistics. The $t_{max}$ was described utilizing minimum, median, and maximum value as well as frequency counts for each value.<br>For each of the primary PK parameters, $AUC_{\tau,ss}$, $C_{max,ss}$, and $A_e$ of lacosamide and metformin, logarithmically (natural log) transformed data were analyzed using analysis of variance (ANOVA). Ratios were calculated for each group and for both groups pooled. For all ratios, the corresponding 90% confidence intervals were provided.<br>Untransformed primary parameter $t_{max}$ was analyzed using the same methods mentioned above. Instead of the ratios, the differences "lacosamide+metformin" – "lacosamide" and "metformin+lacosamide" – "metformin" were calculated. |

b(4)

An overview of the dosing schedules for the 2 groups is given below:

| | Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group 1 | Lacosamide | x | | xx | xx | xx | xx | xx | xx | xx | x | | | | |
| | Metformin | | | | | | | xxx | xxx | xxx | xxx | xxx | xxx | xxx | x |
| Group 2 | Lacosamide | | | | | | | xx | xx | xx | xx | xx | xx | xx | x |
| | Metformin | x | | xxx | xxx | xxx | xxx | xxx | xxx | xxx | x | | | | |

Lacosamide was administered twice daily in the morning and the evening (t=0h and 12h). Metformin were given three times a day at 0, 6 and 12 hours

Lacosamide and metformin tablets were administered prior to meals with 240mL tap water. On Days 1, 6, 10, and 14, subjects were fasting for at least 10 hours before the administration of trial medication in the morning. After the administration of trial medication on these days, the following restrictions applied:
Group 1: On Days 1 and 6, subjects remained fasting until 4 hours after administration of trial medication. On Days 10 and 14, subjects remained fasting until 6 hours after administration of trial medication.
Group 2: On Days 1, 6, and 10, subjects remained fasting until 6 hours after administration of trial medication. On Day 14, subjects remained fasting until 4 hours after administration of trial medication.

**Study Rationale:** Lacosamide is a new substance that is being developed for the treatment of epileptic seizures and neuropathic pain. Neuropathic pain can be caused by diabetes and thus, a co-medication of an oral antidiabetic drug may be possible. Therefore, this interaction trial with metformin, one of the most frequently prescribed oral antidiabetic drug in the US and in Europe, was performed to evaluate the effect of lacosamide on the pharmacokinetics of metformin and vice versa and to assess the necessity of dosage adjustment.

*Reviewer's Note: Both lacosamide and metformin are mainly renally cleared. There may be a drug interaction potential at the transport level.*

**Dose selection:** The proposed therapeutic doses of lacosamide are 50 — ng twice daily. The chosen dosage of 200 mg lacosamide administered twice daily represents a clinically relevant dose. b(4)

The dosages chosen in this trial (200 mg lacosamide administered twice daily and 500 mg metformin administered 3 times daily) mirror typical average clinically relevant doses. Metformin was chosen because it does not lead to hypoglycemia in subjects with normal blood glucose levels. This is relevant because healthy subjects participated in this study.

**Sample Collection:** In both treatment groups, sampling for PK profiling (blood and urine) was done under single dose conditions, under steady-state conditions for the combined treatment, and under steady-state conditions for the unique treatment with lacosamide and metformin,

respectively. In addition, blood samples were drawn throughout the study to evaluate trough levels.

**Sample Analysis:** The concentrations of lacosamide and SPM 12809 were determined by means of a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method in plasma (Validation Report No. 613-02) and urine (Validation Report No. 585-02). The LOQ for both LCM and SPM 12809 in plasma was 0.01 μg/mL and in urine was 0.2 μg/mL. See tables below for summary of analytical data.

Plasma:

| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of Correlation 'r' | Precision of Slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.2 - 4.9 | 98.8 - 101.0 | 1.00000 | 2.1% |
| SPM 12809 | 0.2 – 5.6 | 97.9 - 102.0 | 1.00000 | 2.3% |

Urine:

| Reference compounds | Precision [%] | Accuracy [%] | Coefficient of Correlation 'r' | Precision of Slope 'b' |
|---|---|---|---|---|
| SPM 927 | 0.5 - 2.7 | 94.7 - 107.0 | 0.99902 | 2.7% |
| SPM 12809 | 0.9 - 4.6 | 95.6 - 106.5 | 0.99898 | 3.0% |

**Subjects:** Sixteen subjects were enrolled in this trial and all completed the study. Only healthy male White subjects were enrolled (Table 1).

**Table 1. Demographic Data.**

| Parameter | Statistic | Group 1 (N=8) | Group 2 (N=8) |
|---|---|---|---|
| Age (years) | Mean±SD (range) | 34.4±7.9 (23-44) | 28.8±8.6 (20-44) |
| Body height (m) | Mean±SD (range) | 1.82±0.07 (1.70-1.91) | 1.76±0.03 (1.72-1.80) |
| Body mass index ($kg/m^2$) | Mean±SD (range) | 24.21±2.37 (21.3-28.3) | 22.74±2.25 (19.9-26.2) |
| Body weight (kg) | Mean±SD (range) | 80.11±9.34 (68.3-95.3) | 70.40±6.57 (61.0-78.7) |

SD=standard deviation
Note: Group 1 started with lacosamide on Day 1; Group 2 started with metformin on Day 1

**Pharmacokinetic Results:**

*Effect of metformin on steady-steady lacosamide and SPM 12809 PK:*
Trough concentrations ($C_{trough}$) of lacosamide determined from predose blood samples show that steady-state conditions were reached on Day 6 in Group 1 and on Day 10 in Group 2.

Pharmacokinetic profiles of lacosamide and SPM 12809 were determined on the days given below to compare treatment with lacosamide alone with the combined lacosamide+metformin treatment:
- Day 6: lacosamide alone in Group 1
- Day 10: combined lacosamide+metformin treatment in both groups
- Day 14: lacosamide alone in Group 2

Data were analyzed "by group and treatment" and "by treatment." For the by-treatment analysis, data from the 2 groups were pooled: Group 1/Day 6 and Group 2/Day 14 for the treatment "lacosamide alone" and Group 1/Day 10 and Group 2/Day 10 for "lacosamide+metformin."

PK parameters of lacosamide and SPM 12809 by group and treatment and by treatment are shown in Table 2 and Table 3, respectively. Mean $AUC_{\tau,ss}$ and $C_{max}$ of lacosamide in Group 1 was slightly increased when lacosamide was administered in combination with metformin compared with administration of lacosamide alone. In Group 2, mean values of AUC for the 2 treatments were similar. Mean $AUC_{\tau,ss}$ and $C_{max,ss}$ of the main metabolite of lacosamide, SPM 12809, were slightly increased in both groups when lacosamide was administered in combination with metformin compared with administration of lacosamide alone (Table 2).

**Table 2. Pharmacokinetic parameters of lacosamide and SPM 12809 – by group and treatment.**

| Parameter (unit) | Group | Lacosamide | | SPM 12809 | |
|---|---|---|---|---|---|
| | | alone (N=8) | +metformin (N=8) | alone (N=8) | +metformin (N=8) |
| | | Geometric mean (CV %) | | | |
| $AUC_{\tau,ss}$ | Group 1 | 68.87 (23.27) | 75.50 (23.26) | 11.26 (47.65) | 14.25 (39.47) |
| (µg/mL*h) | Group 2 | 85.40 (10.84) | 87.79 (10.05) | 11.08 (71.12) | 12.41 (63.16) |
| $C_{max,ss}$ | Group 1 | 8.601 (20.14) | 9.829 (19.42) | 1.003 (49.28) | 1.255 (39.60) |
| (µg/mL) | Group 2 | 9.877 (11.54) | 10.102 (6.99) | 0.982 (70.36) | 1.093 (62.61) |
| $A_{e(0-12)}$ [a] | Group 1 | 83.63±22.01 | 68.49±17.559 | 55.72±24.35 | 58.71±19.78 |
| (mg) | Group 2 | 80.58±29.53 | 70.87±18.232 | 45.26±19.60 | 49.23±21.26 |
| $t_{max,ss}$ [b] | Group 1 | 0.5 (0.5-1.5) | 0.5 (0.5-1) | 3.5 (0.5-8) | 3.0 (0.5-6) |
| (h) | Group 2 | 0.5 (0.5-1.5) | 1.0 (0.5-1.5) | 2.0 (0.5-6) | 2.0 (1.5-6) |
| $t_{1/2}$ [c] (h) | Group 1 | 11.40 (22.76) | 11.83 (26.56) | 22.98 (42.15) | 18.11 (29.93) |

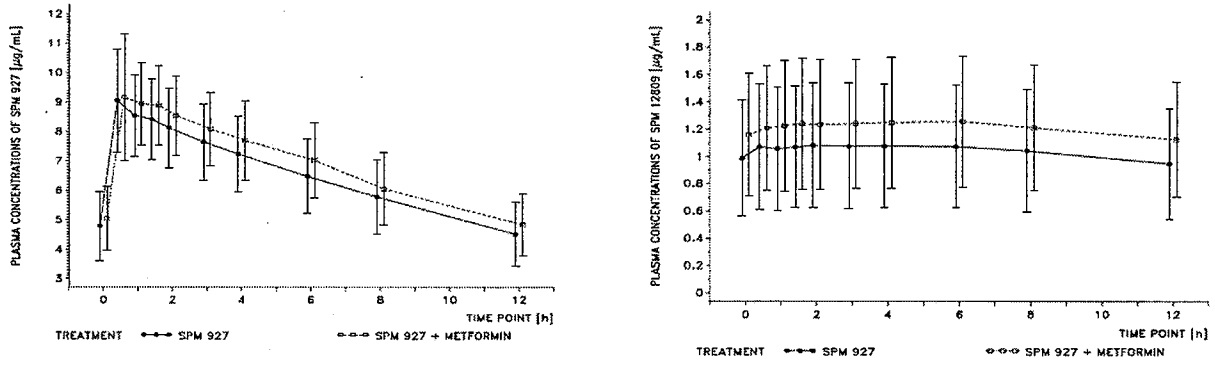
CV=coefficient of variation

Note: Group 1 started with lacosamide on Day 1; Group 2 started with metformin on Day 1.
Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0\text{-}\tau)}$ in post-text tables and listings.
[a] Arithmetic mean±standard deviation
[b] Median (range)
[c] $t_{1/2}$ was determined for Group 1 after single-dose treatment on Day 1 ("lacosamide alone") and after combined treatment with metformin on Day 10 ("lacosamide+metformin").

**Table 3. Pharmacokinetic parameters of lacosamide and SPM 12809 – by treatment.**

| Parameter (unit) | Lacosamide | | SPM 12809 | |
|---|---|---|---|---|
| | alone (N=16) | +metformin (N=16) | alone (N=16) | +metformin (N=16) |
| | Geometric mean (CV %) | | | |
| $AUC_{\tau,ss}$ (µg/mL*h) | 76.69 (20.81) | 81.41 (18.97) | 11.17 (57.61) | 13.30 (50.77) |
| $C_{max,ss}$ (µg/mL) | 9.217 (17.40) | 9.965 (14.12) | 0.9922 (57.91) | 1.171 (50.53) |
| $A_{e(0\text{-}12)}$ [a] (mg) | 82.11±25.21 | 69.68±17.34 | 50.49±22.03 | 53.97±20.43 |
| $t_{max,ss}$ [b] (h) | 0.5 (0.5-1.5) | 0.5 (0.5-1.5) | 2.5 (0.5-8) | 2.5 (0.5-6) |
| $t_{1/2}$ [c] (h) | 11.40 (22.76) | 11.83 (26.56) | 22.98 (42.15) | 18.11 (29.93) |

PK profiles of lacosamide and SPM 12809 by treatment are shown in Figure 1. Mean plasma concentrations of lacosamide and SPM 12809 were slightly higher after the combined treatment compared with the treatment with lacosamide alone.




**a. Lacosamide** **b. SPM 12809**

**Figure 1. Mean plasma concentrations of lacosamide (a) or SPM 12809 (b) at steady state with and without co-administration of metformin (arithmetic mean±SD, N=16) – by treatment.**

Data were analyzed "by group and treatment" and "by treatment." For the by-treatment analysis, data from the 2 groups were pooled: Group 1/Day 10 and Group 2/Day 10 for "lacosamide+metformin" and Group 2/Day 6 and Group 1/Day 14 for "metformin alone."

$AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin were slightly lower in Group 1 and slightly higher in Group 2 when metformin was administered in combination with lacosamide compared with administration of metformin alone.

*Reviewer's Note:* *The data seem to suggest a sequence effect which could not be explained.*

Mean $A_{e(0-6)}$ of metformin was slightly increased when metformin was administered in combination with lacosamide compared with administration of metformin alone in both groups.

When combined data by treatment, there was no difference between metformin alone and metform plus lacosamide treatment groups (Table 7).

**Table 6. Pharmacokinetic parameters of metformin – by group and treatment.**

| Parameter (unit) | Group | Metformin | |
|---|---|---|---|
| | | alone (N=8) | +lacosamide (N=8) |
| | | Geometric mean (CV %) | |
| $AUC_{\tau,ss}$ (µg/mL*h) | Group 1 | 4595 (17.81) | 3986 (21.36) |
| | Group 2 | 3641 (20.40) | 4347 (19.27) |
| $C_{max,ss}$ (µg/mL) | Group 1 | 1026 (22.12) | 900.5 (24.44) |
| | Group 2 | 802.8 (25.80) | 941.3 (20.80) |
| $A_{e(0-6)}$ [a] (mg) | Group 1 | 168.8±45.77 | 189.4±83.82 |
| | Group 2 | 144.9±50.84 | 165.0±49.5 |
| $t_{max,ss}$ [b] (h) | Group 1 | 3.0 (1.5-3) | 2.5 (1.5-4) |
| | Group 2 | 2.0 (1-2) | 2.0 (1-4) |
| $t_{1/2}$ [c] (h) | Group 2 | 3.7 (11.44) | 4.5 (35.35) |

CV=coefficient of variation
Note: Group 1 started with lacosamide on Day 1; Group 2 started with metformin on Day 1.
Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-tz)}$ in post-text tables and listings.
[a] Arithmetic mean±standard deviation
[b] Median (range)
[c] $t_{1/2}$ of metformin was determined only for Group 2 for the single-dose treatment on Day 1 ("metformin alone") and the combined treatment with lacosamide on Day 10 ("metformin+lacosamide).

**Table 7. Pharmacokinetic parameters of metformin – by treatment**

| Parameter (unit) | Metformin | |
|---|---|---|
| | alone (N=16) | +lacosamide (N=16) |
| | Geometric mean (CV %) | |
| $AUC_{\tau,ss}$ (µg/L*h) | 4090 (22.18) | 4163 (20.16) |
| $C_{max,ss}$ (µg/L) | 907.3 (26.59) | 920.7 (22.02) |
| $A_{e(0-6)}$ (mg) [a] | 156.9±48.34 | 177.2±67.68 |
| $t_{max,ss}$ (h) [b] | 2.0 (1.0-3.0) | 2.0 (1.0-4.0) |
| $t_{1/2}$ (h) [c] | 3.711 (11.44) | 4.497 (35.35) |

CV=coefficient of variation
Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-tz)}$ in post-text tables and listings.
a Arithmetic mean±standard deviation
b Median (range)
c $t_{1/2}$ of metformin was determined for Group 2 only (N=8).

PK profiles of metformin by treatment are shown in Figure 2. Mean plasma concentrations of metformin were comparable after the combined treatment compared with the treatment with metformin alone.

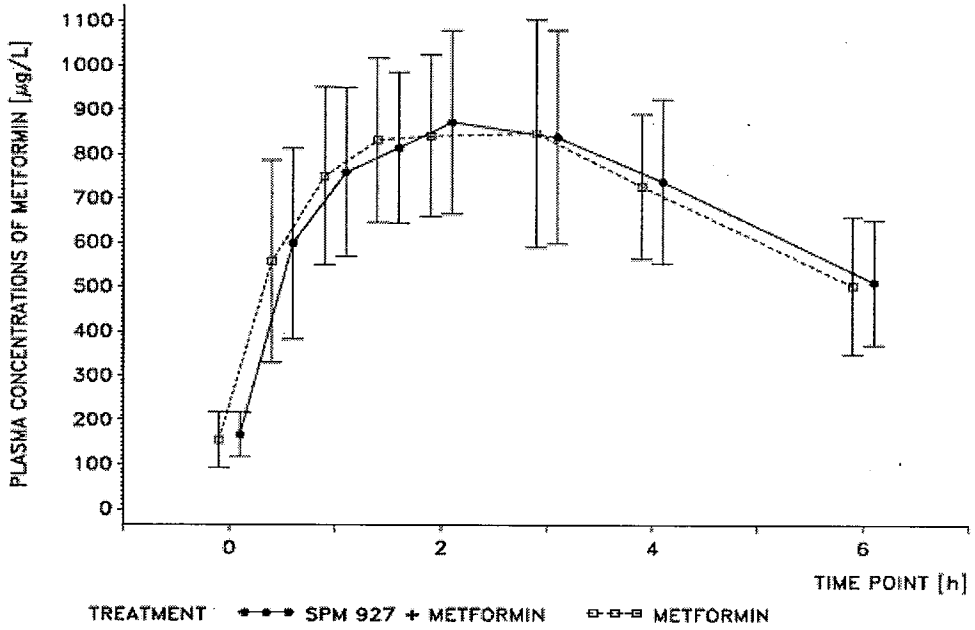



**Figure 2. Mean plasma concentrations of metformin at steady state with and without co-administration of lacosamide (arithmetic mean±SD, N=16) – by treatment.**

The ratios and 90% CIs for $AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin by group and treatment and by treatment are shown in Table 8 and Table 9, respectively.

**Table 8. ANOVA results for primary pharmacokinetic parameters of metformin – by group and treatment.**

| Parameter | Group | Number of subjects | Ratio "metformin+lacosamide"/"metformin" | |
|---|---|---|---|---|
| | | | Estimate | 90% confidence interval |
| $AUC_{\tau,ss}$ | Group 1 | N=8 | 0.8675 | (0.773, 0.973) |
| | Group 2 | N=8 | 1.1939 | (1.064, 1.339) |
| $C_{max,ss}$ | Group 1 | N=8 | 0.8782 | (0.768, 1.004) |
| | Group 2 | N=8 | 1.1725 | (1.026, 1.340) |

For Group 1, ratios for $AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin were below 1 and the lower boundaries of the 90% CIs were outside the generally accepted bioequivalence range of 80-125%.

For Group 2, ratios for $AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin were above 1 and the upper boundaries of the 90% CIs were outside the generally accepted bioequivalence range of 80-125% (Table 8).

**Table 9. ANOVA results for primary pharmacokinetic parameters of metformin – by treatment**

| Parameter | Number of subjects | Ratio "metformin+lacosamide"/"metformin" | |
|---|---|---|---|
| | | Estimate | 90% confidence interval |
| $AUC_{\tau,ss}$ | N=16 | 1.0177 | (0.938, 1.104) |
| $C_{max,ss}$ | N=16 | 1.0147 | (0.923, 1.115) |

ANOVA=analysis of variance
Note: $AUC_{\tau,ss}$ is referred to as $AUC_{(0-\tau)}$ in post-text tables and listings.

The results of the by-treatment analysis (N=16) indicate that the pharmacokinetics of metformin were not influenced in a clinically relevant manner by co-administration of lacosamide (Table 9).

**Safety Summary:** No death or serious AE occurred during the course of the trial. The most common AEs were hypoesthesia, paraesthesia, and dizziness (these AEs occurred only during lacosamide multiple-dose treatment or combined lacosamide+metformin treatment with exception of 1 AE of paraesthesia which was reported after lacosamide single-dose treatment) as well as nausea and diarrhea (these AEs occurred only during metformin multiple-dose treatment or combined metformin+lacosamide treatment).

**Discussion and Conclusions:**

- Although the exposure of lacosamide and SPM 12809 were slightly higher in the presence of metformin, the difference did not seem to be clinically relevant as 90% CIs were within 80-125% bioequivalent boundary.

- For metformin, the 90% CIs for the ratio "metformin+lacosamide"/"metformin" of $AUC_{\tau,ss}$ and $C_{max,ss}$ did not meet the bioequivalence criteria when Group 1 and Group 2 were analyzed separately (analysis by group and treatment, N=8). For example, $AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin for the treatment "metformin alone" were higher when subjects received combined treatment prior to treatment with metformin alone (Group 1) in comparison with combined treatment after treatment with metformin alone (Group 2). This indicates that the pharmacokinetics of metformin may be influenced by the order in which the treatments "metformin+lacosamide" and "metformin alone" were administered. The magnitude of changes (either increase or decrease) in metformin exposure is not considered to be clinically relevant.

- For metformin, when data from both groups were combined, there was no effect of lacosamide on metformin PK.

*4.2.5.4 Oral Contraceptive—Study SP599: A study of the potential pharmacodynamic and pharmacokinetic interaction of SPM 927 (harkoseride) with Microgynon® in healthy female subjects*

---

| | |
|---|---|
| **Title of the trial:** | A study of the potential pharmakodynamic and pharmacokinetc interaction of SPM 927 (harkoseride) with Microgynon® in healthy female subjects |
| **Investigators:** | Principal investigator: [redacted]<br>Subinvestigators: [redacted] |
| **Trial center:** | [redacted] |
| **Publication (reference):** | Not applicable. |
| **Trial period:** | Date of first enrollment: November 27, 2000<br>Date of last subject completed: June 12, 2001 — **Clinical Phase:** I |
| **Objectives:** | The primary objective was to evaluate the effect of SPM 927 on the suppression of ovulation by Microgynon®.<br>Additional objectives were: To evaluate the pharmacokinetics, safety and tolerability of SPM 927 and to evaluate the effect of SPM 927 on the pharmacokinetics of Microgynon®. |
| **Methodology/Design:** | This was an open-label, one-arm trial in healthy female subjects. During cycle 1 normal ovulation was confirmed. The capability of Microgynon®, to suppress ovulation in these subjects was evaluated during cycle 2. The pharmacodynamic and pharmacokinetic interaction of SPM 927 with Microgynon® was evaluated during cycle 3. |

**Treatment schedule**

| Trial Period | Time period | Medication | Days |
|---|---|---|---|
| Eligibility assess-ment | Within 28 days before start of cycle 1 | None | – |
| Cycle 1 | Day 1(first day of menstruation) - day 28 | None | – |
| Cycle 2 | Day 1(first day of menstruation) - day 28 | Microgynon® | 1-21 |
| Cycle 3 | Day 1 - day 22 | Microgynon® | 1-21 |
| | | SPM 927 (2x200 mg, 1x200 mg) | 3-12 (3-11, 12) |
| Follow-up | Day 22 of cycle 3 | None | 1 |

b(4)

| | |
|---|---|
| **Number of subjects:** (total and for each treatment, age and sex): | A total of 40 healthy premenopausal women were enrolled, with at least 30 planned to complete the trial. 31 subjects completed the trial and 9 subjects dropped out. No dose changes occurred.<br>**Number of subjects, withdrawals and completers** |

| | Eligibility assess-ment | Cycle 1 | Cycle 2 | Cycle 3 | Follow-up |
|---|---|---|---|---|---|
| Intended | 40 | 40 | 37 | 32 | 31 |
| With-drawals | – | 3 | 5 | 1 | – |
| Completed | 40 | 37 | 32 | 31 | 31 |

| | |
|---|---|
| **Diagnosis and criteria for inclusion:** | Healthy premenopausal women, age between 18 and 40 years, normal body weight (50-100 kg according to BMI 20-30 kg/m$^2$), non-smokers, were included after giving written informed consent. |
| **Test product, dose, mode of administration, batch No:** | SPM 927: 100 mg capsules given in oral doses of 200 mg twice a day (daily dose 400 mg) from day 3 to day 11 and once a day on day 12 (daily dose 200 mg) of cycle 3, batch No: WE 11559<br>Microgynon®: 1 sugar coated tablet (daily dose) containing: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel, batch No: WE 11585<br>Microgynon® was administered once-a-day from day 1 to day 21 of cycles 2 and 3. |
| **Reference product, dose, mode of administration, batch No:** | Not applicable |
| **Duration of treatment:** | The duration of the trial was approximately 3 months, i.e., a 1-month treatment-free cycle followed by 2 months of treatment. |
| **Criteria for evaluation:** | Primary target variable:<br>Pharmacodynamics: Progesterone serum concentration on day 21 of cycle 3 was measured to indicate suppression of ovulation. A progesterone concentration of<br>< 5.1 nmol/l in serum on day 21 of the cycle was taken as evidence of successfull suppression of ovulation.<br><br>Secondary and other variables:<br>Pharmacokinetics: Plasma concentrations of ethinylestradiol and levonorgestrel under steady state (24-h-profiles on day 12 of cycles 2 and 3). Derived pharmacokinetic parameters, including AUC, $C_{max}$, $t_{max}$.<br>Plasma concentration of SPM 927 under steady state (72-h-profile) on day 12 of cycle 3. Derived pharmacokinetic parameters, including AUC, $C_{max}$, $t_{max}$, $t_{1/2}$, AUMC, MRT, $Cl_{tot}$/f and Vz/f.<br>Safety: Adverse events, vital signs, 12-lead ECG, clinical laboratory. |
| **Statistical methods:** | Statistical evaluation was performed only on data for subjects who entered cycle 2.<br>Safety and demographics: Descriptive statistics (N, mean, median, SD, minimum, maximum).<br>Pharmacodynamics: 90 % confidence interval for the percentage of subjects with suppression of ovulation according to Clopper and Pearson.<br>Pharmacokinetics: ANOVA and confidence intervals for primary pharmacokinetic parameters, descriptive statistics (N, mean, geometric mean, median, SD, geometric SD, minimum, maximum). |

The main objective was to evaluate the effect of SPM 927 on the suppression of ovulation by Microgynon®. The study duration for each individual subject comprised three menstrual cycles. The first evaluation before contraceptive was given to confirm that a normal ovulation occurred in each subject during the first menstruation cycle. Therefore the concentration of progesterone was measured on approximately Day 21 of cycle 1. The concentration of the two active components of the contraceptive were measured during the next cycle, without co-administration of SPM 927 (cycle 2) and during the following menstruation cycle after co-administration of SPM 927 (cycle 3). The efficacy of the oral contraceptive in preventing ovulation was assessed by measuring progesterone serum concentration, which was therefore measured on day 21 of cycles 2 and 3.

Ovulation was assessed on the basis of serum concentration of progesterone. For this assessment a progesterone concentration not exceeding 5.1 nmol/L on day 21 of cycle 3 was taken as evidence of successful suppression of ovulation.

**Sample Collection:**
In cycle 1, no drug analysis was carried out.

In cycle 2 pre-dose levels of ethinylestradiol and levonorgestrel were measured on day 1 (blank) and on day 12. In addition, on day 12 pharmacokinetic profiles were taken with samples at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose.

In cycle 3 the pre-dose level of SPM 927 was measured on Day 3 (blank) and also pre-morning dose on one selected day between Days 9-1 1 for steady state. Pharmacokinetic profiles were taken with samples at Day 12 pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h post-dose and 24, 48, 72 h post-dose (Day 13-1 5).

In cycle 3 pre-dose levels of ethinylestradiol and levonorgestrel were measured on Day 1. Pharmacokinetic profiles were taken with samples at Day 12 pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h post-dose and 24 h post-dose (Day 13).

**Sample Analysis:** Same as Study SP587.

**Subjects:** A total of 40 subjects were enrolled into the trial, of whom 31 completed the trial as scheduled. Withdrawals were not replaced. Subject 8030 (withdrawal due to feverish infection) and subjects 8034 and 8035 (withdrawal due to missing confirmation of ovulation during cycle 1) did not enter cycle 2 and were therefore excluded from the statistical analysis (Table 1).

The mean age of all 37 included subjects was 30.5 years (SD: 5.3), the mean height was 169.5 cm (SD: 6.5), the mean weight was 63.65 kg (SD: 7.26) and the mean BMI was 22.12 kg/m2 (SD: 1.83).

The demographic data of the subgroup of 31 subjects, who completed cycle 3 can be summarized as follows: The mean age of these subjects was 30.1 years (SD: 5.0), the mean height was 169.5

cm (SD: 6.9), the mean weight was 63.78 kg (SD: 7.1) and the mean BMI was 22.1 6 kg/m2 (SD: 1.8).

**Table 1. Number of withdrawals, date, reason and follow-up.**

| Subject | Withdrawals | | Reason | Last administration of Microgynon® | | Follow-up | |
|---|---|---|---|---|---|---|---|
| | Trial period | Day | | Trial period | Day | Trial period | Day |
| 8030 | Cycle 1 | 7 | Due to AE Feverish infection | — | — | Cycle 1 | 7 |
| 8034 | | 27 | No ovulation | — | — | Cycle 1 | 27 |
| 8035 | | 27 | No ovulation | — | — | Cycle 1 | 28 |
| 8013[1] | Cycle 2 | 8 | No ovulation during Cycle 1 | Cycle 2 | 21 | Cycle 2 | 8 |
| 8003 | | 21 | Subject withdrew informed consent | Cycle 2 | 21 | Cycle 3 | 7 |
| 8026 | | 21 | Non-compliance[2] | Cycle 2 | 21 | Cycle 2 | 22 |
| 8040 | | 21 | Subject withdrew informed consent | Cycle 2 | 21 | Cycle 3 | 1 |
| 8019 | | 21 | Non-compliance[2] | Cycle 2 | 21 | Cycle 3 | 19 |
| 8024[3] | Cycle 3 | 1 | Due to AE Eosinophilia | Cycle 3 | 3 | Cycle 3 | 8 |

*Data source: Section 13.1, tables 1.2 to 1.3*

[1] For details of withdrawal of subject 8013 see section 7.2
[2] Due to lack of time
[3] Microgynon® package was not used up by subject 8024. On day 1 of cycle 3 it was decided to exclude her after she had received the Microgynon® package and had left the study center. Because she could not be contacted she was informed on her next visit on day 3 of cycle 3. She left the broached Microgynon® package at the study center.

**Pharmacodynamic Results:**

Progesterone levels were evaluated during cycle 2 in 35 subjects. These 35 subjects received the oral contraceptive during cycle 2 as planned. The successful suppression of ovulation by Microgynon® as confirmed for all of these 35 subjects.

Progesterone levels were evaluated during cycle 3 in 31 subjects who completed the study according to protocol. The successful suppression of ovulation by Microgynon® with coadministration of SPM 927 was confirmed for each of the 31 subjects.

Table 2 summarizes the pharmacodynamic parameters of progesterone level on day 21 of the cycle without medication (cycle 1), after administration of Microgynon® (cycle 2) and after co-administration of SPM 927 (cycle 3) for the 31 subjects who completed the study according to protocol, as well as the difference between the values of cycle 2 and 3.

There was a slight increase of progesterone levels from cycle 2 to cycle 3. All progesterone values were far below 5.1 nmol/L, which was taken as evidence of suppression of ovulation.

**Table 2. Progesterone levels by treatment periods and difference between cycle 2 and 3.**

| | Cycle1 Progesterone level [nmol/l] | Cycle 2 Progesterone level [nmol/l] | Cycle 3 Progesterone level [nmol/l] | Difference of Progesterone levels [nmol/l] between cycle 2 and cycle 3 |
|---|---|---|---|---|
| N | 31 | 31 | 31 | 31 |
| Mean | 35.81 | 0.93 | 1.14 | 0.21 |
| SD | 13.09 | 0.58 | 0.55 | 0.68 |
| Lower 90 % CI | 31.00 | 0.71 | 0.93 | 0.00 |
| Upper 90 % CI | 40.60 | 1.14 | 1.33 | 0.41 |
| Minimum | | | | |
| Median | 38.78 | 0.92 | 1.18 | 0.13 |
| Maximum | | | | |

b(4)

**Pharmacokinetic Results:**

*Effect of multiple dose lacosamide on ethinylestradiol and levonorgestrel PK:*
36 subjects who took Microgynon® during cycle 2 from day 1 to day 21 were evaluated (pharmacokinetics were not evaluated for subject 8013 due to withdrawal on day 8 of cycle 2).

31 subjects were evaluated for cycle 3. A pharmacokinetic profile over 24 hours of plasma concentration of ethinylestradiol and levonorgestrel was taken on day 12 of cycles 2 and 3, i.e. without and with co-administration of SPM 927.

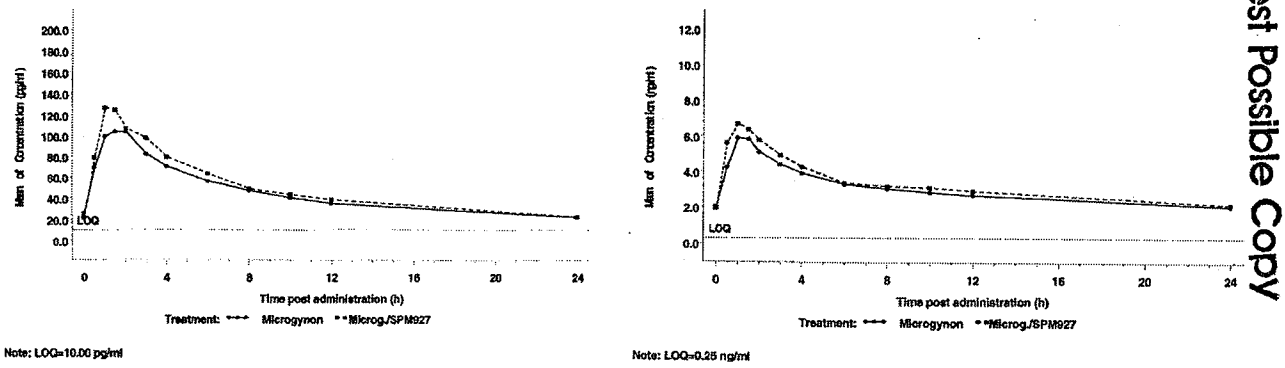
Table 3 and Table 4 summarize the pharmacokinetic parameters of ethinylestradiol and levonorgestrel in plasma on day 12 of cycles 2 (-lacosamide) and 3 (+lacosamdie), respectively. PK profiles of ethinylestradiol and levonorgestrel on day 12 of cycles 2 (-lacosamide) and 3 (+lacosamdie) were shown in Figure 1.

**Table 3. Pharmacokinetic parameters for ethinylestradiol (mean f SD) in plasma on days 12 of cycles 2 and 3.**

| | Cycle 2 (N = 36) | Cycle 3 (N = 31) |
|---|---|---|
| $AUC_{0\rightarrow 24h,ss}$ [pgxh/ml] | 1067 ± 404 | 1173 ± 330 |
| $C_{max,ss}$ [pg/ml] | 116.9 ± 48.8 | 135.7 ± 28.6 |
| $t_{max,ss}$ [h] | 1.5 ± 0.6 | 1.4 ± 0.7 |

**Table 4. Pharmacokinetic parameters for levonorgestrel (mean f SD) in plasma on days 12 of cycles 2 and 3.**

| | Cycle 2 (N = 36) | Cycle 3 (N = 31) |
|---|---|---|
| $AUC_{0\rightarrow 24h,ss}$ [ng·h/ml] | 74.2 ± 21.4 | 80.9 ± 18.5 |
| $C_{max,ss}$ [ng/ml] | 6.7 ± 1.9 | 7.4 ± 1.5 |
| $t_{max,ss}$ [h] | 1.5 ± 1.0 | 1.2 ± 0.6 |




**a. Ethinylestradiol** **b. Levonorgestrel**

**Figure 1. Mean plasma concentrations of ethinylestradiol and levonogestrel with and without coadministration of lacosamide.**

Mean plasma concentrations of both ethinylestradiol and levonorgestrel at steady state were slightly higher when Microgynon® was administered with LCM. Accordingly, $AUC_{\tau,ss}$ and $C_{max,ss}$ of ethinylestradiol and levonorgestrel were slightly increased when Microgynon® was administered with LCM.

A summary of the statistical analysis of $AUC_{\tau,ss}$ and $C_{max,ss}$ for the comparison "Microgynon®+LCM / Microgynon®" is shown in Table 5. The 90% CIs were within the accepted bioequivalence range of (0.8, 1.25) except for the 90% CI for $C_{max,ss}$ of ethinylestradiol which slightly exceeded the upper boundary of the bioequivalence range.

**Table 5. Summary of the statistical analysis for $AUC_{\tau,ss}$ and $C_{max,ss}$ of ethinylestradiol and levonorgestrel – SP599.**

| Parameter | Comparison | Ratio | 90% confidence interval |
|---|---|---|---|
| **Ethinylestradiol** | | | |
| $AUC_{\tau,ss}$ | ethinylestradiol+LCM / ethinylestradiol | 1.113 | (1.052, 1.177) |
| $C_{max,ss}$ | | 1.205 | (1.106, 1.312) |
| **Levonorgestrel** | | | |
| $AUC_{\tau,ss}$ | levonorgestrel+LCM / levonorgestrel | 1.092 | (1.046, 1.140) |
| $C_{max,ss}$ | | 1.120 | (1.053, 1.192) |

*Effect of multiple dose ethinylestradiol and levonorgestrel on lacosamide PK:*
Table 6 summarizes the pharmacokinetic parameters of SPM 927 in plasma on day 12 of cycle 3.

**Table 6. Pharmacokinetic parameters for SPM 927 (mean + SD) in plasma on day 12 of cycle 3 with co-administration of Microgynon®.**

| | | Cycle 3 (N = 31) |
|---|---|---|
| $AUC_{0\rightarrow t,ss}$ | [µgxh/ml] | 248.3 ± 65.7 |
| $AUC_{0\rightarrow 12h,ss}$ | [µgxh/ml] | 113.5 ± 20.7 |
| $AUC_{0\rightarrow 12h,ss,\ normalized}$* | [hxkg/l] | 36.1 ± 7.0 |
| $AUMC_{0\rightarrow 12h,ss}$ | [µgxh²/ml] | 603.1 ± 115.1 |
| $C_{max,ss}$ | [µg/ml] | 13.8 ± 2.2 |
| $C_{max,ss,normalized}$* | [(µg/ml)/(mg/kg)] | 4.4 ± 0.8 |
| $t_{max,ss}$ | [h] | 1.1 ± 0.4 |
| $t_{1/2}$ | [h] | 15.3 ± 2.0 |
| $Cl_{tot}/f$ | [l/h] | 1.8 ± 0.3 |
| $V_z/f$ | [l] | 39.4 ± 5.1 |
| MRT | [h] | 21.3 ± 3.0 |

Exposure of SPM 927 (plasma) in the present study, which were obtained after co-administration of Microgynon, seemed higher (~20-60%) than those observed in previous studies. The following table was extracted from the digoxin interaction study review.

**Table 7. Pharmacokinetic parameters of lacosamide with and without co-administration of digoxin at steady state ("historical comparison").**

| Parameter (unit) | SP644 | SP660 [a] | SP661 [b] | SP602 [c] |
|---|---|---|---|---|
| | Treatment A: Digoxin + lacosamide | Lacosamide alone | | |
| | N=20 | N=8 | N=12 | N=8 |
| $AUC_{(0\text{-}12)ss}$ (µg/mL*h) | 82.50 (13.6) | 68.87 (23.27) | 94.95 (17.3) | 79.05 ±1.18 [d] |
| $C_{max,ss}$ (µg/mL) | 9.46 (11.4) | 8.60 (20.14) | 11.70 (16.2) | 9.10 ±1.16 [d] |
| $C_{min,ss}$ (µg/mL) | 4.869 (17.9) | 3.819 (33.05) | 5.369 (21.1) | n.d. |
| $t_{max,ss}$ (h) | 0.75 (0.50-3.0) | 0.5 (0.5-1.5) | 0.8 (0.5-1.5) | 0.5 (0.5-1.0) |
| $A_{e(0\text{-}12)ss}$ (mg) | 58.85 ±16.12 | 83.63 ±22.01 | 81.59 ±18.69 | n.d. |

Note: Geometric mean and coefficient of variation (%) are shown for $AUC_{(0\text{-}12)ss}$, $C_{max,ss}$, and $C_{min,ss}$; median (range) is shown for $t_{max,ss}$; arithmetic mean±standard deviation is shown for $A_{e(0\text{-}12)ss}$.
n.d.=not determined; PKS=Pharmacokinetic Set
[a] SP660: Data from Group 1 (Day 6) are shown.
[b] SP661: Data from the group of White subjects are shown.
[c] SP602: Data from Group 2 are shown.
[d] Standard deviation of geometric mean is shown because coefficient of variation (%) was not determined.

**Safety Results:** No death or serious adverse events were reported. Two subjects dropped out due to AEs considered not related to administration of SPM 927. The incidence of skin- and CNS-related AEs was higher after co-administration of SPM 927 than during treatment with Microgynon® alone.

**Discussion and Conclusions:**

- There was a slight increase of progesterone levels from cycle 2 to cycle 3 (lower 90 % CI of the difference was 0). Even if the upper 90 % CI was 1.33 nmol/L with a mean increase of 0.21 nmol/L, all progesterone values were far below 5.1 nmol/L. This was taken as evidence of successful suppression of ovulation in all of the investigated subjects. Therefore there is no indication that the co-administration of SPM 927 affects the suppression of ovulation by Microgynon®.

- There was a tendency for increased AUC and Cmax both for ethinylestradiol and levonorgestrel after co-administration of SPM 927 compared to administration of Microgynon® alone. 90% CI for Cmax of ethinyletradiol was outside 80-125% boundary. Because of increased exposure, there is little risk for loss of contraceptive efficacy. The pharmacokinetics results support the results of the pharmacodynamic assessments that show

that SPM 927 does not affect the contraceptive activity of Microgynon®. The 20% increase in ethinylestradiol Cmax should not pose a safety concern.

- Across study comparision showed that exposure of SPM 927 (plasma) in the present study, which were obtained after co-administration of Microgynon®, seemed higher (~20-60%) than those observed in previous studies. The difference may be due to inter-study variability.

## 4.3 Through QT Study Consult Review

**Interdisciplinary Review Team for QT Studies**
**Response to a Request for Consultation: QT Study Review**

| | |
|---|---|
| **INDs** | 57939 |
| **Generic Name** | Lacosamide |
| **Sponsor** | Schwarz |
| **Indication** | Epilepsy/ Diabetic neuropathic pain |
| **Dosage Form** | Immediate release film-coated tablets |
| **Proposed Therapeutic Dose** | 200 - — mg per day |
| **Duration of Therapeutic Use** | Chronic |
| **Maximum Tolerated Dose** | 400 mg bid |
| **Application Submission Date** | 17 Apr 2007 |
| **Review Classification** | TQT study |
| **Date Consult Received** | 23 April 2007 |
| **Clinical Division** | DNP/ HFD-120 |

b(4)

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

In this randomized, positive- and placebo-controlled, parallel study, 247 healthy subjects were administered multiple oral doses of lacosamide 400 mg/day, lacosamide 800 mg/day, moxifloxacin 400 mg/day or placebo. The supratherapeutic dose chosen for this study is only 33% higher than the ——— dose 600 mg/day. The subject exposures in this study may not cover the increases in lacosamide concentrations due to moderate to severe hepatic and renal impairment.

b(4)

At both lacosamide doses, the upper limits of the two-sided 90% CI for the difference between time-matched, baseline-adjusted QTcI in least squares means between the drug and placebo were less than 10 msec, the threshold of regulatory concern identified in the ICH E14 guideline. In fact, the study suggests lacosamide shortens the QTc. At $T_{max}$ on day 6, the mean change after administration of lacosamide 400 mg/day in QTcI from baseline compared to placebo was –9.4 with an upper one-sided 95% CI of –4.2; for 800 mg/day the values were –7.4 and –3.3, respectively. Shortening of the ΔΔQTcI intervals were also observed on day 1 and day 3. The ICH E14 guideline makes no recommendation for the development or labeling of products which shorten the QT interval because adequate data upon which to base a recommendation do not currently exist.

A log-linear mixed-effects model described the relationship between the concentration of lacosamide and its main metabolite SPM 12809 and ΔΔQTcI. The analysis was based on pooling data from all doses (400 mg/day and 800 mg/day) and study days. The mean slope was negative which is consistent with the observed decrease in mean effect on QTcI at $T_{max}$.

The sponsor administered moxifloxacin 400 mg once daily in the morning for 3 days. On day 1 following a single dose, the ΔΔQTcI interval increased by 12 ms (lower 95% confidence bound 8 ms) at 3 hours after dosing which is consistent with the expected effect at $T_{max}$. Obtaining the expected effect implies assay sensitivity; i.e., that the study was adequately designed and conducted to detect a mean effect on the QT interval of 5 ms had it been present.

### 1.2 ADDITIONAL QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- According to the sponsor, the PR interval increased with increasing lacosamide concentrations. The QT-IRT did not review the effects of lacosamide on the PR interval.
- In the sponsor's primary analysis they (1) found the maximum for each individual across all time points within a day; (2) took the average of those maximum values; (3) analyzed the average of the maximum values for each day. They also made a time-matched baseline correction at each time point for each individual. We recommend the following analysis for this parallel study: (1) make a time-matched baseline correction at each time point for each individual; (2) take the average over all subjects at that time point and do the same thing at each time point; (3) difference of the average at each time point is our interest; and (4) perform analysis at each time point. The sponsor also reported this preferred analysis approach and it was verified by the statistical reviewer. Nonetheless, the conclusions from these two approaches did not differ in this instance.
- The administration of the positive control, moxifloxacin, was not optimal in this trial. It is preferable to administer a single dose of 400 mg moxifloxacin on the same day as the effect of lacosamide on the QT was evaluated (i.e., day 6) to establish assay sensitivity. Furthermore, administration of multiple doses of moxifloxacin may confound assessment of its effect because moxifloxacin concentrations accumulate increase the QTc more than is desirable for assay sensitivity. Nonetheless, the sponsor's results for the study as conducted are sufficient to accept the assertion that assay sensitivity was established.
- 247 subjects were enrolled but only 220 completed the study, a dropout rate which is quite high for a healthy subject clinical pharmacology study. 15 subjects (~7% of the total) withdrew for unclear reasons. Ten of the subjects who withdrew due to AE were in the 800 mg/day treatment group. The high number of dropouts as well as the differential dropout rate in the different treatment groups may have affected the quality of the data.

## 2 PROPOSED LABEL

None submitted.

## 3 BACKGROUND

### 3.1 INDICATIONS

b(4)

Treatment of epilepsy and diabetic neuropathic pain [redacted]

### 3.2 DRUG CLASS

Functionalized amino acid

### 3.3 MARKET APPROVAL STATUS

Not approved for marketing in the USA or elsewhere

### 3.4 PRECLINICAL INFORMATION

From the sponsor's study report:

"At a concentration of 3000 µM, lacosamide only inhibited about 7% of the hERG-mediated potassium current ($I_{Kr}$)... (U)nder conditions in which the myocardial cell membrane is depolarized to -70 mV, such as during myocardial ischemia, the inhibitory effect of lacosamide on $Na^+$ current was more pronounced. Under these conditions, lacosamide blocked $Na^+$ currents with an $IC_{50}$ of 67.5 µM and elicited a complete block at 5mM. In mammalian cells expressing the human cardiac $Na^+$ channel lacosamide in the concentration range of 10 to 5000 µM reduced the $Na^+$ current in a concentration dependent fashion."

### 3.5 CLINICAL EXPERIENCE

According to the 29 Aug 2006 IB, approximately 1300 unique subjects with epilepsy and approximately 1631 unique subjects with neuropathic pain have been exposed to lacosamide in both completed and ongoing open-label and double-blind, placebo-controlled trials. Adverse events that appeared to be dose-related include dizziness, nausea, fatigue, ataxia, visual abnormalities, diplopia, vertigo, and nystagmus. The sponsor has not detected any consistent effect on the QT interval. Administration of lacosamide prolongs the PR interval in a dose dependent manner and is associated with first degree AV block.

Two out of 1023 subjects exposed to lacosamide in trials for diabetic neuropathic pain died due to cardiac arrest or ventricular fibrillation. No subjects in trials in partial seizures had cardiac arrest. No episodes of torsade de pointes are reported. The sponsor comments "Since lacosamide doses greater than 400 mg/day may be associated with an increased number of cardiac adverse events compared with <400mg/day doses in diabetic neuropathic pain subjects, ——— b(4)

### 3.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of lacosamide's clinical pharmacology.

**Table 1: Highlights of Clinical Pharmacology**

| | |
|---|---|
| Therapeutic dose | For treatment of Epilepsy: The daily dose is administered in two equally divided doses. The recommended starting dose is 100 mg per day, which should be increased to an initial therapeutic dose of 200 mg per day after one week. Based on individual patient response and tolerability, the dose can be further increased by 100 mg per day every week, to a maximum recommended dose of — mg /day. b(4) |
| Maximum tolerated dose | The maximum tolerated dose in clinical pharmacological trials was 800mg (400mg bid) in multiple dose trials (SP588, SP640) and 600mg in a single |

dose trial (SP587).

The no-observed-adverse-effect-levels (NOAELs) were 60, 90 and 10 mg/kg/day in mice, rats and dogs after once daily oral administration of lacosamide for 3, 6 and 12 months.

Principal adverse events

The frequency of adverse events in clinical pharmacological trials is exemplary shown in the table below for trial SP640.

**Summary of subjects with the most common (≥2% in any group) treatment-emergent adverse events (SS)**

| System organ class<br>Preferred term | Placebo N=62 | LCM 400 mg/day N=60 | LCM 800 mg/day N=71 | Moxifloxacin 400 mg/day N=54 |
|---|---|---|---|---|
| | n (%) | | | |
| **Any system organ class** | | | | |
| Any event | 18 (29.0) | 27 (45.0) | 56 (78.9) | 8 (14.8) |
| **Cardiac disorders** | **2 (3.2)** | **2 (3.3)** | **3 (4.2)** | **1 (1.9)** |
| Palpitation | 2 (3.2) | 2 (3.3) | 3 (4.2) | 1 (1.9) |
| **Ear and labyrinth disorders** | **0** | **0** | **6 (8.5)** | **0** |
| Vertigo | 0 | 0 | 4 (5.6) | 0 |
| **Eye disorders** | **1 (1.6)** | **0** | **15 (21.1)** | **1 (1.9)** |
| Diplopia | 0 | 0 | 7 (9.9) | 0 |
| Vision blurred | 0 | 0 | 6 (8.5) | 0 |
| **Gastrointestinal disorders** | **2 (3.2)** | **10 (16.7)** | **33 (46.5)** | **3 (6)** |
| Nausea | 1 (1.6) | 5 (8.3) | 19 (26.8) | 1 (1.9) |
| Hypoesthesia oral | 0 | 1 (1.7) | 15 (21.1) | 0 |
| Vomiting | 0 | 3 (5.0) | 9 (12.7) | 0 |
| Dry mouth | 0 | 0 | 3 (4.2) | 0 |
| Stomach discomfort | 0 | 0 | 3 (4.2) | 0 |
| **General disorders and administration site conditions** | **2 (3.2)** | **10 (16.7)** | **14 (19.7)** | **0** |
| Feeling drunk | 2 (3.2) | 5 (8.3) | 11 (15.5) | 0 |
| Feeling hot | 0 | 2 (3.3) | 4 (5.6) | 0 |
| Fatigue | 0 | 0 | 2 (2.8) | 0 |
| **Musculoskeletal and connective tissue disorders** | **6 (9.7)** | **4 (6.7)** | **7 (9.9)** | **0** |
| Muscle twitching | 0 | 1 (1.7) | 5 (7.0) | 0 |
| Back pain | 2 (3.2) | 2 (3.3) | 0 | 0 |
| **Nervous system disorders** | **12 (19.4)** | **12 (20.0)** | **49 (69.0)** | **4 (7.4)** |
| Dizziness | 4 (6.5) | 6 (10.0) | 39 (54.9) | 2 (3.7) |
| Headache | 9 (14.5) | 10 (16.7) | 16 (22.5) | 1 (1.9) |

| | | | | | |
|---|---|---|---|---|---|
| | Paresthesia | 1 (1.6) | 0 | 4 (5.6) | 0 |
| | Paresthesia oral | 0 | 0 | 3 (4.2) | 0 |
| | Hypoesthesia | 0 | 1 (1.7) | 2 (2.8) | 0 |
| | **Respiratory, thoracic, and mediastinal disorders** | **2 (3.2)** | **4 (6.7)** | **6 (8.5)** | **1 (1.9)** |
| | Pharyngolaryngeal pain | 2 (3.2) | 2 (3.3) | 3 (4.2) | 1 (1.9) |
| | Nasal discomfort | 0 | 0 | 2 (2.8) | 0 |
| | **Skin and subcutaneous tissue disorders** | **0** | **2 (3.3)** | **5 (7.0)** | **0** |
| | Hyperhidrosis | 0 | 0 | 2 (2.8) | 0 |

LCM = lacosamide; Moxi = moxifloxacin, SS = safety set
Note: n = number of subjects reporting at least 1 AE within the body system/preferred term; % = percentage of subjects among total (N)
Data source: Trial SP640 Table 17.1

The most frequent AEs that lead to drop-out or withdrawal of the Informed Consent were dizziness, nausea and vomiting in a dose-dependent manner. These AEs were regarded as dose limiting.

| | | |
|---|---|---|
| Maximum dose tested | Single Dose | 800 mg |
| | Multiple Dose | 500 bid for 13.5 days (limited tolerability) |
| Exposures Achieved at Maximum Tested Dose | Single Dose (sd) | SP587 (800mg sd, N=9):<br>$C_{max}$: Mean: 18.43µg/ml (26%) [Geometric Mean, CV%]<br>$AUC_{0-\infty}$: Mean: 293.24µg/ml*h (26.5%) [Geometric Mean, CV%] |
| | Multiple Dose (md) | SP588 (500 mg bid, N=4):<br>$C_{max}$: Mean: 15.25µg/ml (1.78-21.80) [Median, range]<br>$AUC_{0-12}$: Mean: 130.39µg/ml*h (14.89-196.26) [Median, range] |
| Range of linear PK | Dose-proportional increase of $C_{max}$ and AUC for doses between 100 mg and 800 mg single dose and 100 mg and 400 mg multiple dose | |
| Accumulation at steady state | Following twice-daily dosing, lacosamide plasma concentration increases with an accumulation factor of approximately 2.3. | |
| Metabolites | 1. Lacosamide (approximately 40% of the administered dose excreted unchanged)<br>2. SPM 12809 (approximately 30% of the dose)<br>3. Polar fraction (approximately 20% of the dose)<br>4. Small amounts of further metabolites (p-hydroxy-, O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and desacetyl-derivatives of LCM) representing 0.5% to 2% of the dose were also found in urine.<br>5. N-carbamoyl-O-ß-D-glucuronide of the desacetyl-metabolite | |

| | | |
|---|---|---|
| Absorption | Absolute/Relative Bioavailability | Absolute bioavailability of the oral formulation: Approximately 100% |
| | Tmax | • Lacosamide - Median (range): 1.00h (1.00-4.00h) [SP640, N=57, after 400mg/day at steady state] • SPM 12809 - Median (range): 12.00h (6.00-24.00h) [SP863, N=34, after 300mg sd] |
| Distribution | Vd/F or Vd | V/F - arithmetic mean ± SD : 1. 54.89 ± 14.08 L (SP587, after 400 mg sd oral lacosamide, N=12) 2. 48.92 ± 10.08 L (SP587, after 800 mg sd oral lacosamide, N=9) 3. 45.12 ± 9.45 L (SP588, after 300 mg sd oral lacosamide, N=14) 4. 57.11 ± 22.66 L (SP588, after 500 mg sd oral lacosamide, N=10) |
| | % protein bound | <15% |
| Elimination | Route | • Primary route: Renal excretion; 40% of dose is eliminated as unchanged lacosamide, 30% as SPM 12809 • Other routes:metabolism (Presumably hepatic, see SP642) |
| | Terminal t½ | • Mean: 13 hours (CV: ~20%) for lacosamide • Mean: 19 hours (CV: ~20%) for SPM 12809 (SP620, after 100mg bid md in healthy male subjects) |
| | CL/F or CL | CL/f – Geometric mean (CV): 2.71 L/h (14.2%) [SP588, N=14, after 300mg sd] 2.40 L/h (14.2%) [SP588, N=12, after 300mg bid md] |
| Intrinsic Factors | Age | $AUC_{\tau,ss,norm}$*: ~ 25% higher AUC in elderly males (≥65 years) compared to young males (≤45 years), ~15% higher AUC in elderly females (≥65 years) compared to young males (≤45 years $C_{max,ss,norm}$*: ~22% higher $C_{max}$ in elderly males (≥65 years) compared to young males (≤45 years) ~25% higher $C_{max}$ in elderly females (≥65 years) compared to young males (≤45 years) * body weight normalized |

| | | |
|---|---|---|
| | Sex | AUCτ,ss:<br>- 13% higher AUC in elderly females (≥65 years) compared to elderly males (≥65 years), after body weight normalization no differences in AUC between elderly females and elderly males<br>$C_{max,ss}$:<br>- 19% higher $C_{max}$ in elderly females (≥65 years) compared to elderly males (≥65 years), after body weight normalization no differences in AUC between elderly females and elderly males |
| | Race | AUCτ,ss:<br>- 10% higher exposure of LCM in Asian and Black compared to White subjects, but similar exposure after body weight normalization within the 3 ethnic groups<br>$C_{max,ss}$:<br>- No difference between Asian, Black and White subjects in mean $C_{max,ss}$ |
| | Hepatic & Renal Impairment | Hepatic Impairment<br>- AUCτ,ss, $C_{max,ss}$: 60%, 50% increased in subjects with moderate hepatic impairment, after body weight normalization the differences were reduced to 50%, 37%<br>- The increase of exposure is mainly caused by coexisting renal impairment<br><br>Renal Impairment<br>$AUC_{(0-tz)}$:<br>- 60% increased in subjects with severe renal impairment (differences were reduced by 10% by body weight normalization)<br><br>- 20-30% increased in subjects with mild and moderate renal impairment (differences were reduced by 10% by body weight normalization)<br>$C_{max}$:<br>- 10-15% increase in subjects with mild, moderate and severe renal impairment |
| Extrinsic Factors | Drug interactions | Phase 1 DDI studies:<br>**1. SP644 (Digoxin)**<br>- No differences for AUC and Cmax of |

| | | |
|---|---|---|
| | | digoxin with and without coadministration of lacosamide<br>- AUC and $C_{max}$ of lacosamide under coadministration with digoxin were comparable to those obtained in previous trials without coadministration of digoxin (historical comparison)<br>**2. SP660 (Metformin)**<br>- Lacosamide: 6% increase of AUC, 8% increase of $C_{max}$ under coadministration with Metformin<br>- Metformin: No differences for AUC and $C_{max}$ under coadministration with lacosamide compared to administration of metformin alone<br>**3. SP601, SP602 (Valproic acid)**<br>- Lacosamide: No differences for AUC and $C_{max}$ under coadministration with VPA compared to administration of lacosamide alone<br>- VPA: No differences for AUC and $C_{max}$ under coadministration with lacosamide compared to administration of VPA alone<br>**4. SP603, SP618 (Carbamazepine)**<br>- Lacosamide: <10% increase of AUC and $C_{max}$ under coadministration with CBZ compared to administration of lacosamide alone<br>- CBZ: A maximum change of 10% of AUC and $C_{max}$ under coadministration with lacosamide compared to administration of CBZ alone<br>**5. SP863 (Omeprazole)**<br>- Lacosamide: 10% increase of AUC and no change of $C_{max}$ under coadministration with omeprazole compared to administration of lacosamide alone<br>- Omeprazole: 10% increase of AUC and $C_{max}$ under coadministration with lacosamide compared to administration of omeprazole alone<br>**6. SP599 (Oral contraceptive)**<br>- Ethinylestradiol: 10% increase of AUC, 20% increase of $C_{max}$ under coadministration with lacosamide compared to administration of ethinylestradiol alone |

| | | |
|---|---|---|
| | | - Levonorgestrel: 10% increase of AUC and $C_{max}$ under coadministration with lacosamide compared to administration of levonorgestrel alone<br>- AUC and $C_{max}$ of lacosamide under coadministration with ethinylestradiol and levonorgestrel were comparable to those obtained in previous trials without coadministration of both drugs (historical comparison) |
| | Food Effects | No differences in $AUC_{(0-tz)}$ and $C_{max}$ in the fed state after a high-fat breakfast and in the fasting state. |
| Expected High Clinical Exposure Scenario | The most likely high exposure scenario will occur in the diabetic neuropathic pain patient with severe renal failure. The proposed labeling for lacosamide [redacted] b(4) | |
| | According to trial SP641, we expect a 60% higher exposure and 15% higher Cmax in this population. This exposure is fully covered by the dosages used in the thorough QT/QTc trial SP640. | |

# 4 SPONSOR'S SUBMISSION

## 4.1 OVERVIEW

The sponsor submitted a thorough QT study.

## 4.2 QT STUDY

### 4.2.1 Title

A double-blind, single-site, randomized, placebo- and positive-controlled, parallel-design trial of the electrocardiographic effects of 400 and 800 mg per day of lacosamide in healthy male and female subjects: a thorough QT trial

### 4.2.2 Protocol Number

SP640

### 4.2.3 Objectives

Primary

Define the effects of lacosamide on the QT/QTc interval.

Secondary

- Explore the relationship between lacosamide plasma concentration and QTc
- Evaluate additional electrocardiographic effects of lacosamide,
- Further investigate the safety and tolerability of lacosamide.

### 4.2.4 Design

#### 4.2.4.1 Description

Double-blind (with respect to placebo and lacosamide), single-site, randomized, placebo- and positive-controlled, parallel-design 'thorough QT study' conducted from 27 Jun 2005 to 27 Oct 2005

For each subject in the placebo and both of the lacosamide treatment groups, the trial consisted of Eligibility Assessment (Day -28 to Day -3), a 9-day in-house period (Day -2 to Day 7) with treatment on Days 1 to 6 and a safety follow-up visit at least 14 days after last administration of trial medication. Subjects in the moxifloxacin group underwent the same visit schedule except their in-house period was 6 days (Day -2 to Day 4) because they were treated only on Days 1 to 3.

Three 12-lead ECGs were downloaded from the Holter-12 flash card at each of the following time points on Day -1, Day 1 (first day of dosing for placebo, moxifloxacin, 400 mg/day lacosamide), and Day 3 (first day of dosing at 800mg/day for subjects in 800 mg/day lacosamide group, last day of dosing for subjects in moxifloxacin group), and Day 6 (last day of dosing for all subjects except those in moxifloxacin group): 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 24 hours. Plasma samples for determination of lacosamide and the main metabolite (O-desmethyl lacosamide, hereafter referred to as SPM 12809) concentrations and pharmacokinetic (PK) analysis were drawn on Day 3 pre morning dose (0 hour), 2 hours post morning dose, and pre evening dose (12 hours); Day 5 pre morning dose (0 hour) and pre evening dose (12 hours); and Day 6 pre morning dose and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours post morning dose.

#### 4.2.4.2 Sponsor's Justification for Design

Not provided.

*Reviewer's comment: The plasma half-life of the unchanged drug is approximately 13 hours and is not altered by different doses or by multiple dosing so administration for several days is needed to attain steady state concentrations.*

#### 4.2.4.3 Controls

The Sponsor used both negative (placebo) and positive (moxifloxacin) controls.

#### 4.2.4.4 Blinding

Moxifloxacin administration was not blinded.

### 4.2.5 Dosing Regimens

#### 4.2.5.1 Treatment Arms

- Placebo 4 tablets bid for 6 days
- Moxifloxacin 400 mg qd for 3 days (days 1-3)
- Lacosamide 400 mg/day (4 x 50 mg tablets bid) for 6 days (days 1-6)
- Lacosamide 400 mg/day (4 x 50 mg tablets bid) for 2 days followed by 800 mg/day (4 x100 mg tablets bid) for 4 days

#### 4.2.5.2 Sponsor's Justification for Doses

b(4)

The clinical dose range is currently anticipated to be 200 to — mg per day. In the Phase 1 study SP588 subjects were assigned to receive 300 mg or 500 mg bid lacosamide dosing for 14 days. During the trial, 7 of 11 subjects of the 500 mg bid dosing group had mild to moderate, mainly CNS-related adverse events (AEs) that resulted in a dosage adjustment to 400 mg bid. This dose was fairly well tolerated by all these subjects. Based on the results of trial SP588, 400 mg bid lacosamide dosing was considered by the sponsor to be the highest dose to be safe and tolerable in healthy subjects. The dose of 400 mg/day of lacosamide is currently being tested in Phase 3 trials.

#### 4.2.5.3 Instructions with regard to meals

The trial medication will be administered with approximately 240 mL tap water. The high oral bioavailability of approximately 95% is not affected by food. During the in-house days, breakfast, lunch, a snack, and an evening meal were served under standardized conditions.

#### 4.2.5.4 Study Assessments

Table 2 provides the schedule for the key interventions and assessments.

**Table 2: Highlights of Schedule of Interventions**

| Trial Phase | Eligibility Assessment | Baseline (Check-in to site) | Treatment Phase | Treatment Phase | Treatment Phase | Discharge |
|---|---|---|---|---|---|---|
| Day(s) | -28 to -3 | -2/-1 | 1 | 2 - 5 | 6 | 7 |
| Administration of trial drug | | | lcm /placebo bid Moxi qd[c] | LCM /placebo bid Moxi qd[c] | LCM / placebo bid | |
| 12-lead ECG from H-12 | | X[d] | X[d] | X[d] (Day 3 only) | X[d] | |
| PK blood samples | | | | X[f] | X[g] | |

c Moxifloxacin group was only treated for 3 days

d ECGs at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 hours postdose on Days -1, 1, 3, and 6.

e Or at time of discontinuation

f Pre morning dose, 2 hours post morning dose, and pre evening dose (Hour 12) on Day 3; Pre morning dose and pre evening dose (Hour 12) on Day 5

g Pre-morning dose (trough level), and 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours post morning dose (Plasma samples were obtained from both placebo and lacosamide subjects on Day 6 to maintain comparable trial conditions and the double blind; except for the pre morning dose and 2 hour samples, PK samples were only analyzed for the lacosamide treatment group.)

#### 4.2.5.5 Sponsor's justification for sampling schedule

The sponsor provided no justification for the sampling schedule.

#### 4.2.5.6 Baseline

Time-matched baseline is used in the primary analysis.

### 4.2.6 ECG Collection

ECGs were obtained digitally using a [redacted] Instrument H-12 ECG continuous recorder. The subjects were semi-recumbent or lying down for 2 hours after administration of trial medication on Days 3 and 6.

The ECGs were stored on a flashcard about every 10 seconds and were not available for review the card was received by the central ECG laboratory and analyzed. Three 12-lead ECGs were downloaded from the H-12 flashcard within 1 minute at each time point. Within each 1-minute interval, the earliest and latest measurable ECGs were selected as well as the measurable ECG closest to 30 seconds. These ECGs were read centrally using high-resolution manual on-screen caliper method with annotations.

It is stated in the Electrocardiographic Methods of the study report (page 1179); "...the cardiologist is blinded to treatment, however all subject identifiers and visit information defined for the study is displayed... (The) cardiologists are not aware of the trial design (e.g. visit schedule, dosing, etc)...(and) do have access to the ECG demography for the ECG they are evaluating and associated ECGs for that subject."

*Reviewer's comment: The QT-IRT recommends that the reader be blinded to subject identifiers, treatment, time, and day (i.e., Day -1; Day 1) to minimize bias and review of all ECGs from a particular subject by a single reader on one day in hopes of minimizing intra-reader variability. The description provided suggests that readers are effectively blinded. However, the ECGs in this study probably were not read in a single day. Since this reviewer is unaware of data actually indicating that intra-reader variability is minimized by having all ECGs read in a single day, this lack is not a major review item.*

### 4.2.7 Sponsor's Results

#### 4.2.7.1 Study Subjects

247 healthy subjects were randomized; 60 subjects in the lacosamide 400 mg/day group, 71 subjects in the lacosamide 800 mg/day group, 62 subjects in the placebo group, and 54 subjects in the moxifloxacin group. All randomized subjects received treatment with trial medication. Of the 247 randomized subjects, 220 (89.1%) completed the trial. Subjects who withdrew were replaced with the next subject of the same gender that qualified for randomization. Patient disposition is summarized in Table 3.

APPEARS THIS WAY
ON ORIGINAL

b(4)