CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM TO FILE

b(4)

Dissolution Specification or Lacosamide Tablets (NDA 22-253 and NDA —— ~

b(4)

NDA number (submission date)	NDA 022-253 and —— (September 28, 2007)
Drug name, substance, dosage form and strength	Vimpat, Lacosamide film-coated tablets (50-, 100-, 150-, 200-, 250- and 300-mg)
Sponsor	Schwarz Biosciences, Inc. Research Triangle Park, NC
Clinical Division	Division of Neurology Products and Division of Anesthesia, Analgesia and Rheumatology Products

The purpose of this memorandum to file is to clarify and consolidate the ONDQA recommendation for dissolution specification for the lacosamide tablets.

In my April 4, 2008, dated review of this submission, I had provided the following section to support dissolution specification for lacosamide tablets:

> The Sponsor has shown in multiple media that lacosamide tablets are highly soluble (pH range 1 to 7.5) and based on the submitted data, the following dissolution method for the lacosamide tablets is acceptable:
>
> USP Apparatus 2 (Paddle)
> Test medium: 0.1 N HCl, 900 mL
> Temperature: 37° C ± 0.5°C
> Paddle rotation speed: 50 rpm
> Q:—— at 30 min
>
> b(4)
>
> For the CMC review including complete product quality assessment and specification for the lacosamide dosage forms, please see Dr. Prafull Shiromani's review.
>
> In the NDA, although lacosamide dissolution testing was carried out at 50 rpm paddle rotation speed, the Sponsor proposes ——rpm for the dissolution specification, however, consistent with the submission, the Sponsor should maintain the original paddle speed of 50 rpm for dissolution testing.

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Consistent with the above comments, the primary quality reviewer, Dr. Prafull Shiromani, had also requested additional information from the Sponsor (including those related to dissolution and stability testing of the lacosamide tablets).

The Sponsor responded to the IR letter on April 29, 2008. Dr. Shiromani's May 20, 2008, dated review, encompassing evaluation of the updated dissolution test results obtained at both 50 rpm and — rpm (as part of the updated 24 month stability data from twelve primary stability batches and additional supportive data), indicates that the Q value of — at 30 min with a paddle speed of 50 rpm is acceptable for ensuring product quality. b(4)

This reviewer agrees with Dr. Prafull Shiromani's extensive chemistry review of the dissolution test results obtained from stability batches. The Q value of — at 30 min is acceptable (instead of — at 30 min) based on dissolution test results that indicate that as long as the test is carried out with a — paddle speed (50 rpm vs. — rpm) and according to the above test conditions (USP Apparatus 2, and 900 mL of 0.1 N HCl media), the dissolution test is suitable for quality assessment of the lacosamide tablets. b(4)

For product specification of the lacosamide tablets, including in vitro dissolution, please see Dr. Shiromani's May 20, 2008, dated Chemistry Review.

Signature:

Arzu Selen, Ph.D.
Associate Director, Biopharmaceutics
Office of New Drug Quality Assessment

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/s/

Arzu Selen
6/27/2008 11:15:26 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDAs	**22-253,** — b(4)
Submission Dates:	9/28/2007; 11/26/2007; 12/13/2007; 5/27/2008
Type:	505(b)(1)
Generic Name:	Lacosamide
Brand Name:	VIMPAT
Drug Class:	Other antiepileptics
Proposed Indications:	**NDA 22-253:** For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older **NDA** — . For the management of neuropathic pain associated with diabetic peripheral neuropathy b(4)
Clinical Divisions:	**NDA 22-253:** Neurology Products (DNP) **NDA** — . Anesthesia, Analgesia and Rheumatology Products (DAARP)
OCP Division:	Clinical Pharmacology 2 (DCP2)
Reviewers:	Lei Zhang, Ph.D. Emmanuel O. Fadiran, R.Ph., Ph.D.
Team Leader:	Suresh Doddapaneni, Ph. D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Dosage Form:	Film Coated Tablets
Strengths:	50, 100, 150, 200, 250, and 300 mg
Route of Administration:	Oral
Propsoed Dosing regimens:	**NDA 22-253:** Starting dose is 100 mg (50 mg twice daily) and the recommended maintenance dose of lacosamide is 200-400mg per day. Maximum dose is — mg/day. [redacted] b(4)
Applicant:	Schwarz Biosciences, Inc
Relevant IND:	IND —
Type of Submission; Code	505 (b)(1); 1S b(4)

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Lacosamide (LCM) is a new molecular entity being developed as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older and for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN). The proposed dose regimen is 50 to 200 mg twice daily, not to exceed — mg per day. b(4)

The precise mechanism by which lacosamide exerts its antiepileptic and analgesic effects in humans remains to be fully elucidated. Preclinical experiments suggest that lacosamide has a dual mode of action: In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing while exerting no effects on physiological neuronal excitability. Additionally, lacosamide binds to collapsing response mediator protein-2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. CRMP-2 expression was found to be dysregulated in the brain of epileptic patients as well and in the ———————————

There are — dosage forms of lacosamide products: film-coated tablet, solution for injection, ——— Tablet is for epilepsy (NDA 22-253) and DPN ——— indications, and the later — formulations are for epilepsy ——— (NDA 22-254 ——— b(4)

The epilepsy indication (NDA 22-253, NDA 22-254 ——— is reviewed by the Division of Neurology Products (DNP) and the neuropathic pain indication (NDA —) is reviewed by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP).

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-253 and NDA —— Clinical Pharmacology information submitted on September 28, 2007 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert. b(4)

1.2 PHASE IV COMMITMENT

To better understand drug interaction potential for lacosamide, the Sponsor is recommended to

provide the following data as a Phase 4 commitment:

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

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

More than 30 *in vivo* pharmacokinetic studies and *in vitro* metabolism/transport study reports have been submitted in support of clinical pharmacology for this NDA.

These studies were cross-referenced among [redacted] NDAs and were reviewed by four reviewers in OCP: Dr. Tandon in DCP1 (NDAs 22-253, 22-254, [redacted]) and Dr. Zhu in Pharmacometrics (NDAs 22-253 and [redacted]), and Drs. Fadiran and Zhang in DCP2 (NDAs 22-253 and [redacted] This review by Drs. Fadiran and Zhang comprehensively covers all the general Clinical Pharmacology aspects pertinent to NDAs 22-253 and [redacted] and has adequate detail to stand on its own. Detailed reviews of the individual studies are captured in this review, reviews by Dr. Tandon (DCP1) and Dr. Zhu (Pharmacometrics). The following table lists the location of reviews of individual studies. b(4)

Brief Description	Study Number	Location of Review
In vitro study reports		
In vitro metabolism/Transport		DCP2
In vitro inhibition/induction		DCP2
Plasma protein binding		DCP2
In vivo metabolism		
^{14}C-radiolabel study in human	SP619	DCP2
Dose-proportionality		
Single dose-tablets	SP835	DCP2
	SP587	DCP2
Multiple dose-tablets	SP836	DCP2
	SP588	DCP2
Single dose-IV	SP834	DCP1
Special populations		
Renal Impairment	SP641	DCP2
Hepatic Impairment	SP642	DCP2
CYP2C19 EM vs. PM	SP643	DCP1
Age and gender	SP620	DCP2
Race	SP661	DCP2
Drug interaction studies		
Digoxin	SP644	DCP2
Metformin	SP660	DCP2
Omeprazole	SP863	DCP2
Oral contraceptive	SP599	DCP2

Effect on valproic acid	SP601	DCP1
Valproic acid effect	SP602	DCP1
Cabamezapine effect	SP603	DCP1
Effect on cabamezapine	SP618	DCP1
Comparative BE		
[redacted]	SP657	DCP1
iv solution vs. tablet	SP658	DCP1
iv solution vs. tablet	SP645	DCP1
Food effect-tablet	SP600	DCP2
Population PK in healthy subjects and patients		Pharmacometrics
Exposure-Response Analysis		Pharmacometrics
QT	SP640	QT-IRT

DCP2: this review; DCP1: Dr. Tandon's review (dated June 10, 2008); Pharmacometrics: Dr. Zhu's review (dated June 5, 2008); QT-IRT: Appendix 4.3 of this review (dated July 25, 2007).

Absorption, Distribution, Metabolism and Elimination

Following oral administration, lacosamide is absorbed with a Tmax of approximately 0.5 to 4 hours after dosing. The elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of repeated administration (twice daily). Pharmacokinetics of lacosamide is dose proportional at the therapeutic dose range. Food does not affect lacosamide PK.

Absolute bioavailability of lacosamide was determined to be ~100% indicating an almost complete absorption of LCM after oral administration.

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

In vitro incubation with human liver microsomes, hepatocytes, kidney microsomes, and plasma showed a low metabolic turnover of lacosamide (<4% at 4 hours). Two metabolites, SPM 12809 (desmethyl) and SPM 6912 (desacetyl) were found in trace quantities (<3%). However, the human radiolabeled ADME study (SP619) suggested that lacosamide was metabolized *in vivo*. Only 40% of unchanged LCM was recovered in urine and about 30% of the dose was recovered in urine as SPM 12809, the major metabolite. Another 20% of dose was recovered as a polar fraction. Investigations with [^{14}C]-lacosamide labeled either at the carboxylic or at the benzylic carbon atom suggest that the polar fraction may be a desbenzylamine derivative. SPM 12809 is not pharmacologically active. Levels of SPM 12809 in plasma and urine were confirmed in several PK studies. Exposure of SPM 12809 is approximately 10% of the parent compound in plasma.

The maximum plasma concentration of SPM 12809 occurs later than the parent, LCM. At steady state, T_{max} of SPM 12809 at steady state occurs between 1.8 and 4 hours after dosing (range: 0.5-12 hours). The terminal half-life of SPM 12809 is between approximately 15 and 23

hours and is not altered by different doses or by multiple dosing.

The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. The Sponsor determined that lacosamide is a CYP2C19 substrate and formation of SPM 12809 is via this pathway. The Sponsor did not study other CYP isoforms in the recombinant systems. The role of other enzymes in lacosamide metabolism is unknown. POP-PK data analysis showed a 20% decrease in exposure in the presence of cabamazepine, phenytoin or phenobarbital which may indicate an induction effect. As of note, all these three drugs are CYP3A inducers. Whether the data imply that CYP3A may be involved in metabolism of LCM remains to be determined. The Sponsor conducted an interaction study with carbamazepine in healthy subjects and data did not show effect of carbamazepine on lacosamide. Metabolite, SPM 12809, was not monitored in the study.

Renal is the major clearance pathway for lacosamide as 95% of dose was recovered in urine either as lacosamide (40%) or metabolites.

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

Special Populations

Renal Impairment (Study SP641): Systemic exposure of lacosamide (AUC) increased with increasing degree of renal impairment. Renal function was classified based on estimated creatinine clearance according to the FDA 1998 renal guidance. Mean AUC increased 27%, 23%, and 59% in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function, respectively (Table 1). AUC values were more variable for patients with severe renal impairment, and AUC in some patients were 2-fold higher than AUC in subjects with normal renal function. Renal clearance of lacosamide decreased with increasing degree of renal impairment. For C_{max}, only a slight difference was observed. The terminal half-life of lacosamide in plasma ($T_{1/2}$) was prolonged in subjects with severe renal impairment (approximately 18 hours) in comparison with normal renal function subjects (approximately 13 hours).

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

Results from subjects with endstage renal disease (ESRD) receiving hemodialysis showed that under a 4-hour dialysis starting 2.5 hours after dosing, $AUC_{(0\text{-}tz)}$ of LCM and SPM 12809 was approximately 50% lower in ESRD subjects receiving hemodialysis after a single oral dose of 100 mg LCM compared with dosing on a dialysis-free day (Table 1). 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 (i.e., Tmax < 2.5 hours).

Pharmacokinetics of LCM was similar in severe renal impairment patients and ESRD patients.

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

For patients with ESRD who are on hemodialysis, due to the decreased plasma concentrations of lacosamide under dialysis conditions, dose adjustment needs 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.

Hepatic Impairment (Study SP642): Plasma concentrations of lacosamide were approximately 50-60% higher in the subjects with moderate hepatic impairment (Child-Pugh Classification B) compared to subjects with normal hepatic function (Table 1). Half-life was prolonged and the amount of lacosamide excreted into urine within 0-12 hours after administration was reduced by approximately 20-30% in the subjects with hepatic impairment. The T_{max} was comparable between the 2 groups. Plasma concentrations of the main metabolite of lacosamide, SPM 12809, were approximately 40-50% lower in subjects with hepatic impairment compared to healthy subjects.

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

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

Gender and Age (Study SP620): Exposure of LCM was higher in elderly male and female subjects compared with young male subjects. In terms of age effect, elderly male subjects showed ~30% higher AUC than young male subjects. In terms of gender effect, elderly female subjects showed ~15% higher AUC than elderly male subjects (Table 1). When taking body weight differences into considerations, the difference between genders went away, however, there was 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 that leads to increased lacosamide exposure.

Age and sex do not influence exposure in patients with partial seizure based on population PK analyses results.

b(4)

Race (Study SP661): 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%) (Table 1). 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 and Cmax were approximately 30% to 50% lower in Asian and Black subjects compared with White subjects. This difference is not considered clinically relevant because the exposure of SPM 12809 is lower in Blacks and Asians compared with White subjects and SPM 12809 has no known pharmacological activity.

No dose adjustment is needed based on race.

Pediatric Patients: The pharmacokinetic profile of lacosamide in pediatric patients has not been established. The Sponsor requested a deferral for initiating the pediatric development program for lacosamide [redacted] b(4)

CYP2C19 Polymorphism (Study SP643): Plasma concentrations of lacosamide were comparable (not more than 10% difference) between poor metabolizers (PMs) (n=4) and extensive metabolizers (EMs) (n=8) (Table 1), however, there were noticeable differences (75-80% difference) between PMs and EMs with respect to AUCs of the metabolite SPM 12809. PM and EM were classified based on genotype. PMs were homozygous for nonfunctional alleles and EMs were either heterozygous or homozygous for wild-type alleles. . The data confirmed that CYP2C19 is involved in SPM 12809 formation. As level of SPM 12809 is low compared to lacosamide, dose adjustment based on CYP2C19 genotype is not needed.

Refer to Table 1 for summary of findings on effect of intrinsic factors on lacosamide exposure.

Table 1. Influence of intrinsic factors on lacosamide exposure.

Intrinsic Factors		Lacosamide doses evaluated	Cmax Ratio (90% CI) Compare to respective controls	AUC Ratio (90%CI) Compare to respective controls	Dosage Adjustment	
					Sponsor's proposal	Reviewer Recommen-dation
Renal Impairment Control: Normal (CLcr >80 mL/min)	Mild (CLcr 50-80 mL/min)	100 mg single dose	1.0955 (0.8972, 1.3375)	1.2682 (1.0601, 1.5172)	No dose adjustment is necessary	same
	Moderate (CLcr 30-50 mL/min)		1.1356 (0.9301, 1.3866)	1.2247 (1.0237, 1.4651)	No dose adjustment is necessary	same
	Severe (CLcr < 30 mL/min)		1.1223 (0.9192, 1.3703)	1.5903 (1.3293, 1.9025)		The maximum dose should be kept — of maximum dose recommend for patients with normal organ function. b(4)
	ESRD patients on hemodialysis (CLcr < 30 mL/min)	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	Treatment B/Treatment A 0.8757 (0.7573, 1.0126)	Treatment B/Treatment A 0.5369 (0.5060, 0.5697)		The maximum dose should be kept — of maximum dose recommend for patients with normal organ function. b(4)
Hepatic Impairment Control: Normal	Moderate (Child-Pugh B)	100 mg twice daily	1.50 (1.30-1.73)	1.61 (1.36-1.91)		The maximum dose in mild and — hepatic impairment patients should be kept — of maximum dose recommend for patients with normal organ function. b(4)

					/ /	Lacosamide should be contraindicated in patients with severe hepatic impairment.
Age Control: Young (Male)	Elderly (Male)	100 mg twice daily	1.29 (1.16, 1.43)	1.33 (1.18, 1.50)	No dose adjustment is necessary	No dose adjustment but dose titration with caution.
Gender Control: Male (Elderly)	Female (Elderly)		1.19 (1.07, 1.31)	1.13 (1.00, 1.28)	No dose adjustment is necessary	Same
Race Control: White	Black	200 mg twice daily	1.0100 (0.8883, 1.1483)	1.1037 (0.9795, 1.2435)	No dose adjustment is necessary	Same
	Asian		1.0282 (0.9043, 1.1690)	1.1150 (0.9896, 1.2562)	No dose adjustment is necessary	Same
CYP2C19 Polymorphism	CYP2C19 PM vs. CYP2C19 EM	200 mg twice daily	1.03	1.10	No dose adjustment is necessary	Same

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Drug interactions

The potential for drug interactions was evaluated in eight *in vivo* clinical pharmacology studies which incorporated an evaluation of the relevant *in vitro* DDI results (omeprazole), drugs that can be expected to be coadministered with lacosamide (digoxin, metformin, oral contraceptive, cabamazepine, and valproic acid).

Potential for lacosamide to affect other drugs	**Potential for other drugs to affect lacosamide**
Digoxin, Oral contraceptive, Omeprazole, Metformin, Cabamazepine, Valproic Acid,	Omeprazole, Metformin, Cabamazepine, Valproic Acid

Cabameazpine and valproic acid interaction studies were mainly for the epilepsy indication and were reviewed by Dr. Tandon under NDA 22-253.

Lacosamide did not show to affect PK of digoxin and omeprazole (Table 2). Lacosamide increases Cmax of ethinylestridiol in oral contraceptive (~20%) (Table 2). Its effect on metformin wasl dependent on the sequence in which the subjects received metformin. The effect of lacosamide on metformin PK showed different trend for Group 1 (started with lacosamide on Day 1) and Group 2 (start with metformin on Day 1): Group 1 showed decreased exposure and Group 2 showed increased exposure of metformin in the presence of lacosamide (Table 2). PD

of metformin was not studied. However, these changes were in the range of 15 to 20% and the overall magnitude of change on metformin PK is not considered clinically relavent.

Metformin did not affect PK of lacosamide (Table 3). 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 polymorphism study).

Refer to Table 2 for summary of findings on effect of lacosamide on concomitant drugs exposure and Table 3 for summary of effect of concomitant drugs on lacosamide exposure.

Table 2. Influence of lacosamide on concomitant drug exposure.

Concomitant Medication		Concomitant medication dose	Lacosamide doses evaluated	Cmax Ratio (90% CI) . w/wo lacosamide	AUC Ratio (90%CI) w/wo lacosamide	Dosage Adjustment	
						Sponsor's proposal	Reviewer Recommen-dation
Omeprazole		40 mg single dose	300 mg twice daily	1.1049 (0.9793, 1.2466)	1.0976 (0.9963, 1.2092)	No dose adjustment is necessary	same
Digoxin		0.25 mg QD	200 mg twice daily	1.0487 (0.9592, 1.1465)	1.0241 (0.9792, 1.0709)	No dose adjustment is necessary	same
Metformin		500 mg three times a day (0, 6, and 12 hr)	200 mg twice daily	Group 1 0.8782 (0.768, 1.004) Group 2 1.1725 (1.026, 1.340)	Group 1 0.8675 (0.773, 0.973) Group 2 1.1939 (1.064, 1.339)	None	None
Oral Contra-ceptive (Micro-gynon)	ethniyl estradiol	0.03 mg 3 cycles	200 mg twice daily (the 3rd cycle)	1.205 (1.106, 1.312)	1.113 (1.052, 1.177)	No dose adjustment is necessary	same
	levonor gestrel	0.15 mg 3 cycles	200 mg twice daily (the 3rd cycle)	1.120 (1.053, 1.192)	1.092 (1.046, 1.140)	No dose adjustment is necessary	same
Valproate		titrated from 300 to 600 mg	titrated from 100 to 400 mg	1.01 (0.97-1.07)	1.04 (0.99-1.09)	No dose adjustment is	same

					necessary	
Carbamazepine	titrated from 200 to 400 mg	titrated from 200 to 400 mg	0.91 (0.87-0.98)	0.88 (0.84-0.92)	No dose adjustment is necessary	same
Carbamazepine-epoxide			0.95 (0.87-1.05)	0.97 (0.89-1.04)		

Table 3. Influence of concomitant drugs on lacosamide exposure.

Concomitant Medication	Concomitant medication dose	Lacosamide doses evaluated	Cmax Ratio (90% CI) w/wo lacosamide	AUC Ratio (90%CI) w/wo lacosamide	Dosage Adjustment	
					Sponsor's proposal	Reviewer Recommen-dation
Omeprazole	40 mg QD	300 mg single dose	0.9958 (0.9474, 1.0467)	1.1330 (1.1015, 1.1654)	No dose adjustment is necessary	same
Metformin	500 mg three times a day (0, 6, and 12 hr)	200 mg twice daily	Group 1 1.1427 (1.044, 1.250) Group 2 1.0228 (0.935, 1.119)	Group 1 1.0964 (1.062, 1.132) Group 2 1.0280 (0.996, 1.061)	No dose adjustment is necessary	same
Valproate	titrated from 300 to 600 mg	400 mg	1.01 (0.96-1.07)	1.00 (0.98-1.03)	No dose adjustment is necessary	same
Carbamazepine	titrated from 200 to 400 mg	400 mg	1.075 (0.98-1.170)	1.011 (0.96-1.065)	No dose adjustment is necessary	same

QTc Prolongation Potential (QT-IRT consult review)

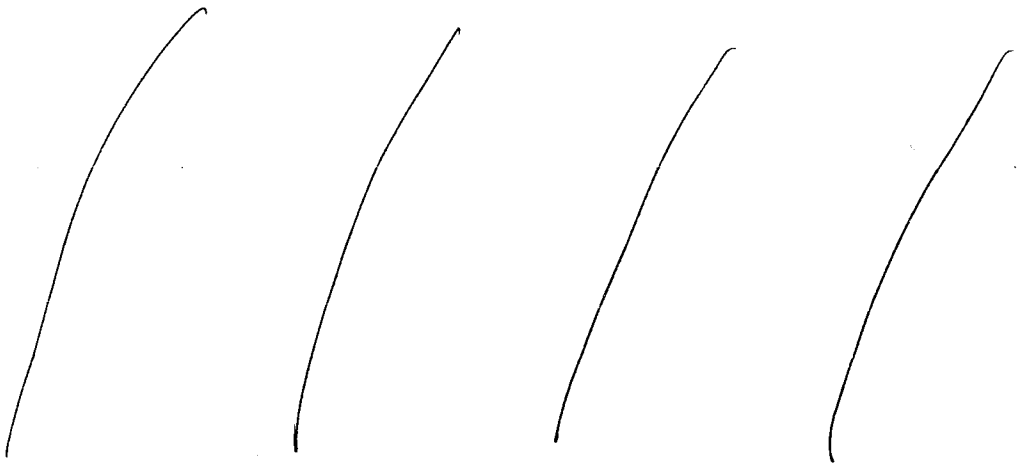
The Sponsor conducted a Thorough QT study (SP640). The study report was reviewed by the QT-IRT (interdisciplinary team) under IND 57, 939. Their review found that both lacosamide and SPM 12809 did not prolong QTc but shortened QTc. For lacosamide, at T_{max} on day 6, the mean change after administration 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. As of note, the supra-therapeutic dose chosen for this study is only 33% higher than the highest proposed dose of 600 mg/day. The subject exposures in this study may not cover the increases in lacosamide concentrations due to moderate to severe hepatic or severe renal impairment (AUC increased 50-60%).

Population PK and Exposure-Response (PM review)

Population PK has been conducted in both healthy and patient populations. PK parameters are comparable between healthy subjects and patient population.

Across the pivotal trials for DPN,



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See PM review for more details.

BCS Classification

Data were submitted to support a BCS class 1 classification of the drug and was deemed appropriate. Based on BCS class 1 classification, biowaiver could be granted for in vivo bioequivalence studies for different immediate-release oral dosage forms. As of note, multiple oral dosage forms were used in various clinical trials during the product development. The sponsor requested waiver of BE studies based on the argument that

a) Lacosamide is a Biopharmaceutics Classification System (BCS) class 1 drug.
b) Lacosamide drug product is rapidly soluble (>80% dissolution in < 15 minutes)

Refer to ONDQA review for details.

A Clinical Pharmacology briefing (Required Inter-Divisional Level) was held on May 27, 2008.

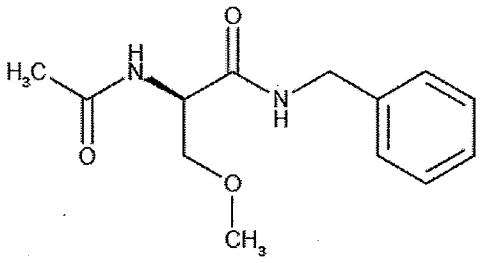
2 QUESTION BASED REVIEW

(Reviewer's Note: Lacosamide, LCM, SPM 927, harkoseride, and ADD 234037 are used interchangeably in the review.)

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physicao-Chemical Properties of Lacosamide.

Drug Name	Lacosamide
Chemical Name	(R)-2-Acetamido-N-benzyl-3-methoxypropionamide (IUPAC)
Structure and Molecular Formula	 $C_{13}H_{18}N_2O_3$
Molecular Weight	250.3
Chirality	Lacosamide is the single dextrorotatory (R)-enantiomer. The chiral purity of the drug substance is not less than ⎯ (R)-enantiomer.
pKa	No pK_a within pH 1.5 – 12 is observed
Partition coefficient	Log $P_{octanol\text{-}water}$ = 0.25
Appearance	White to light yellow powder
Melting Range	140°C – 146°C
Hygroscopicity	Lacosamide is not hygroscopic and does not form any hydrates.
Polymorphism	Four crystalline forms and one amorphous form of lacosamide were identified. Except for the thermodynamically most stable form 1 and form 2, the other forms are not stable under normal conditions and are not formed / present in lacosamide drug substance. b(4)
Solubility	It is soluble in ⎯ soluble in water and slightly soluble in ethanol and acetonitrile.

The aqueous solubility of forms 1 and 2 as a function of pH is presented in Table 2.1.1.2. ⎯ The calculated dose solubility volume of the highest dose b(4) strength of the immediate release tablet (300 mg) is:

300 mg/ ⎯ mg/mL = ⎯ mL

as lamotrigine, phenytoin, and carbamazepine enhance fast inactivation with no or small effects on slow inactivation.

In addition, it has been shown that LCM interacts with collapsing response mediator protein 2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth. The interaction of LCM with CRMP-2 represents a second mode of action of LCM.

b(4)

Proposed indications for NDA 22-253 and NDA — as per the proposed label from the Sponsor):

b(4)

1.2 Partial-Onset Seizures

TRADENAME (lacosamide) tablets — are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older. TRADENAME (lacosamide) injection — when oral administration is temporarily not feasible.

b(4)

2.1.3 What are the proposed dosage recommendations by the Sponsor and route of administration of lacosamide for the proposed indication?

Lacosamide tablets are taken orally.

b(4)

Proposed dosage and administration for NDA 22-253 and NDA — (as per the proposed label from the Sponsor):

2.1 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

b(4

2.2 Partial-Onset Seizures

b(4)

b(4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

With regard to Clinical Pharmacology, more than 30 *in vivo* pharmacokinetic studies and *in vitro* metabolism/transport study reports have been submitted in support of this NDA. PK, absorption, distribution, metabolism, and excretion (ADME) characteristics of lacosamide were studied. Effect of intrinsic factors including renal and hepatic impairment, CYP2C19 genotype, age, gender, and race on the PK of lacosamide was determined. In addition, drug interaction between lacosamide and drugs such as digoxin, metformin, omeprazole, and oral contraceptives were studied. QT/QTc prolongation potential of lacosamide was assessed. Finally, population PK and PK/PD analyses were conducted in both healthy subjects and DNP patients, and source of inter-individual variability in the pharmacokinetics of lacosamide and the exposure-response relationships for effectiveness were investigated.

To support safety and efficacy evaluation for the indication of neuropathic pain associated with diabetic peripheral neuropathy, the sponsor conducted 4 primary efficacy trials: 3 parallel-design, randomized, double-blinded, placebo-controlled, parallel-group, fixed-dose trials, SP742, SP743, and SP768, and 1 randomized withdrawal, crossover study, SP746. In addition, there are 4 long-term open-label safety studies.

b(4)

tudies SP742 and SP768 were conducted in the U.S. and Study SP743 was conducted in Europe.

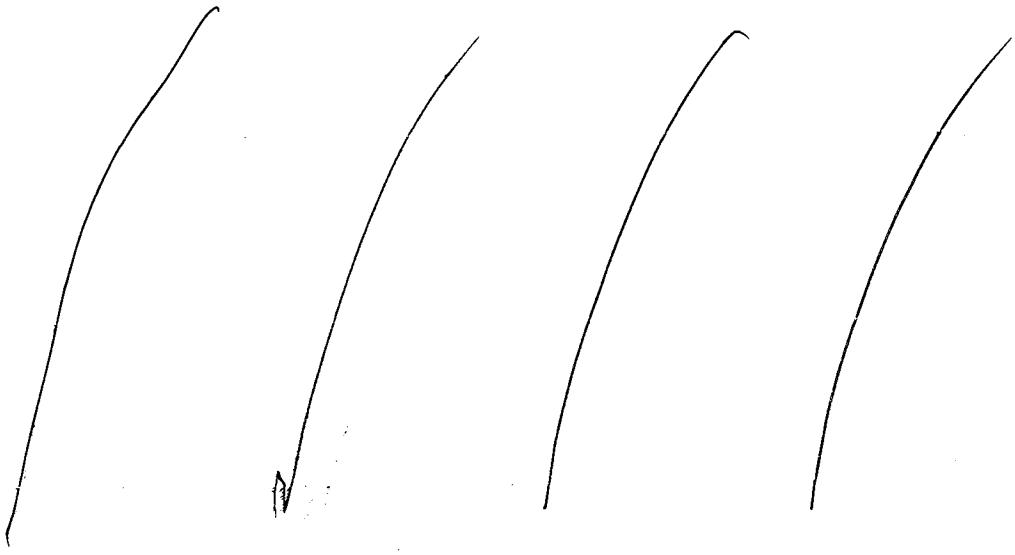
Table 2.2.1.1. Primary efficacy trials in subjects with DNP.

Study	Design	Dose and Number of Patients	Duration (stable dose)	Titration Schedule
SP742 US N=370	Randomized, double-blinded, placebo-controlled	200 mg/day: 93 400 mg/day: 91 600 mg/day: 93 Placebo: 93	12 wks	For each dose group, dose starts at 100mg/day and titrates upwards over 6 weeks to 100mg/day at weekly intervals or until reaching maintenance dose
SP743 Europe N=357	Randomized, double-blinded, placebo-controlled	400 mg/day: 150 ("fast" vs. "slower" titration) 600 mg/day: 133	12 wks	400 mg- • Scheme A (slow): 100mg/day x 3 wks, then weekly titration in 100mg increments to the target dose

		Placebo: 74		• Scheme B (fast): Dose increase in increments of 100 mg/week 600 mg- Dose increase in increments of 100 mg/week
SP768 US N=468	Randomized, double-blinded, placebo-controlled	200 mg/day: 141 400 mg/day: 125 600 mg/day: 137 Placebo: 65	12 wks	For each dose group, dose starts at 100mg/day and titrates upwards over 6 weeks to 100mg/day at weekly intervals or until reaching maintenance dose

Enrollment criteria were similar among three trials. Subjects were male or female, 18 years of age or older. Subjects had symptoms of painful distal diabetic neuropathy for 6 months to 5 years and had a diagnosis of diabetes mellitus (Type I or Type II). Subjects had HbA1c levels <12% with optimized diabetic control (best effort to achieve best control) for at least 3 months prior to Visit 1 and also had at least moderate pain (average pain intensity during the 7 days prior to Visit 2 of ≥4 out of 10 on an 11-point Likert pain scale). Patients enrolled did not have other chronic pain conditions.

2.2.2 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy studies? What is the clinical outcome in terms of safety and efficacy?



b(4)

The most frequent drug-associated treatment emergent adverse event (TEAE) occurring in all LCM-treated subjects were dizziness and nausea. Dizziness occurred at a lower incidence in

b(4)

subjects with DNP (16.3%) than subjects with partial-onset seizures (30.6%) whereas the incidence of nausea was similar across the 2 populations (10.3% in DNP and 11.4% in partial-onset seizures). There were 12 deaths with two deaths possibly drug-related: one patient died from entricular fibrillation and the other died from cardiac arrest. Elevated AST and ALT also have been observed at higher doses.

Refer to Medical Officer (Dr. Pokrovnichka) and Statistics Reviewer (Dr. Meaker)'s review for clinical outcome in terms of efficacy and safety.

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

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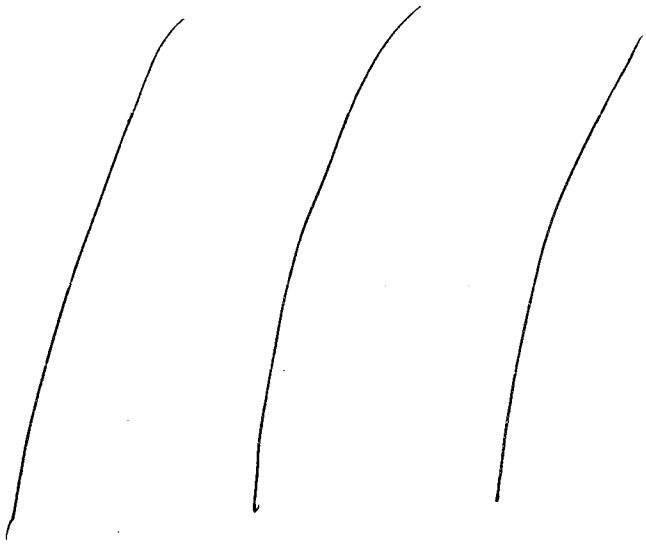

b(4)

Figure 2.2.3.1. Exposure-Response Relationship for Lacosamide in Treating Patients with Painful Distal Diabetic Neuropathy by the End of Titration Phase (Blue Line) and by the End of Maintenance Phase (Red Line) (Responder's Analysis).

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Dizziness was the most frequent drug-associated treatment emergent adverse event (TEAE) and the incidence of dizziness was related to dose. Other CNS drug-associated TEAEs, such as tremor, balance disorder, and coordination abnormal, also were dose related. The incidence of drug-associated TEAEs, such as nausea and vomiting, was similar in the placebo, LCM 200mg/day, and LCM 400mg/day groups and higher in the LCM 600mg/day group.

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Table 2.2.4.1. Incidence of drug-associated TEAEs (DNP Pool S1).

Preferred term	Placebo N=291	LCM 200mg/day N=234	LCM 400mg/day N=426	LCM 600mg/day N=363	LCM Total N=1023
	n (%)				
Common					
Dizziness	15 (5.2)	17 (7.3)	58 (13.6)	92 (25.3)	167 (16.3)
Nausea	18 (6.2)	22 (9.4)	29 (6.8)	54 (14.9)	105 (10.3)
Tremor	3 (1.0)	7 (3.0)	25 (5.9)	34 (9.4)	66 (6.5)
Somnolence	4 (1.4)	9 (3.8)	18 (4.2)	21 (5.8)	48 (4.7)
Vertigo	5 (1.7)	2 (0.9)	14 (3.3)	26 (7.2)	42 (4.1)
Balance disorder	0	4 (1.7)	11 (2.6)	20 (5.5)	35 (3.4)
Other[a]					
Headache	28 (9.6)	20 (8.5)	37 (8.7)	38 (10.5)	95 (9.3)
Fatigue	12 (4.1)	8 (3.4)	33 (7.7)	28 (7.7)	69 (6.7)
Vomiting	5 (1.7)	7 (3.0)	9 (2.1)	17 (4.7)	33 (3.2)
Coordination abnormal	2 (0.7)	2 (0.9)	8 (1.9)	10 (2.8)	20 (2.0)
Diplopia	0	0	0	9 (2.5)	9 (0.9)

LCM=lacosamide; TEAE= treatment-emergent adverse event
a Additional terms that led to discontinuation of 1% or greater of subjects in DNP Pool S1.
Data source: ISS Table NP.6.13.1

2.2.5 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure-response relationships?

Yes, the Sponsor measured the appropriate moieties in clinical pharmacology studies.

To determine PK characteristics of lacosamide, both lacosamide and its major metabolite, SPM 12809, were monitored in plasma and urine in most clinical pharmacology studies. SPM 12809 is not pharmacologically active.

Other appropriate moieties were also monitored in drug interaction studies.

Please refer to Section 2.6 Analysis for analytical details.

2.2.6 Is the dose/dosing regimen proposed by the sponsor acceptable?

b(4)

2.2.7 *Does lacosamide prolong QT or QTc interval?*

No. Both lacosamide and SPM 12809 did not prolong QTc but shortened QTc. 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.

The thorough QT/QTc study (SP640) is a 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 [redacted] 600 mg/day. The subject exposures in this study may not cover the increases in lacosamide concentrations due to moderate to severe hepatic or severe renal impairment (AUC increased 50-60%). 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.

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.

See the QT-IRT consult review for more details (Appendix 4.3).

2.2.8 *What are the PK characteristics of lacosamide and its metabolite, SPM 12809?*

2.2.8.1 *What are single dose and multiple dose PK parameters of lacosamide?*

Single Dose

Following single dose administration, the maximum plasma concentration of lacosamide was reached between 1 and 4 hours after dosing and the mean terminal half-life was estimated to be approximately 13 hours at all doses. Data from Study SP835 are shown in Table 2.2.8.1.1. C_{max} and AUC were dose proportional for doses 100 through 800 mg.

Table 2.2.8.1.1. Pharmacokinetic parameters of LCM following single administrations of 100, 200, 400, and 600mg LCM in healthy male subjects (Study SP835).

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

LCM=lacosamide
a One of the 6 subjects randomized to 600mg LCM did not receive trial medication.

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

Table 2.2.8.1.2. Pharmacokinetic parameters of LCM following single and multiple administrations of 300 and 500mg LCM in healthy male subjects (Study SP588).

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

The C_{trough} is approximately 50% to 60% of the corresponding maximum plasma concentration at steady state ($C_{max,ss}$) (Table 2.2.8.1.3).

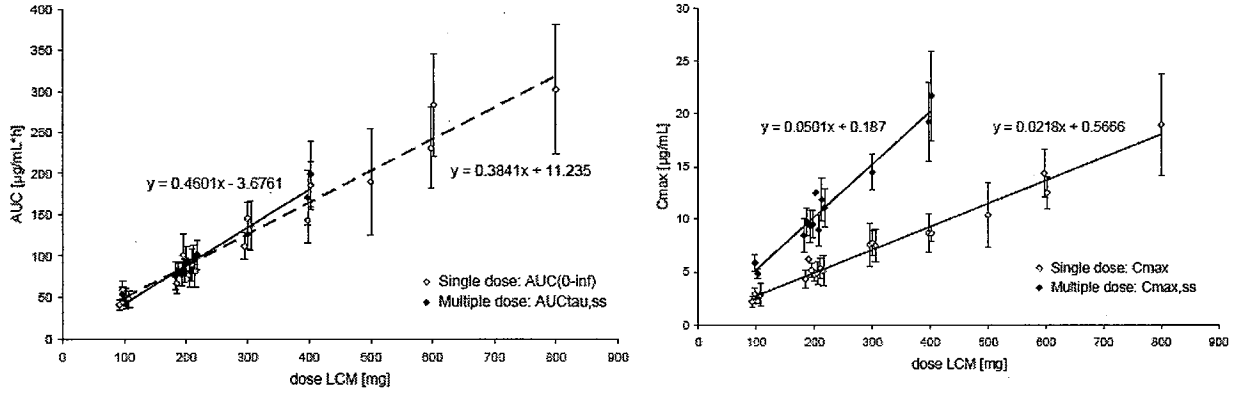
Table 2.2.8.1.3. Trough plasma concentrations of LCM at steady state in healthy subjects – SP603 and SP661.

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

bid=bis in die (twice daily); LCM=lacosamide; SD=standard deviation
a SP603: Data for Sequence Group 2 (starting with LCM prior to coadministration of carbamazepine) are shown.
b SP661: Data for the group of White subjects are shown.

2.2.8.2 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Both AUC and C_{max} increase proportionally with the dose after single- and multiple-dose administration of LCM. Mean values of AUC and C_{max} after single- and multiple-dose administration of different doses of LCM are presented in Figure 2.2.8.2.1.



AUC Cmax

Figure 2.2.8.2.1. Dose-proportional increase of $AUC_{(0-\infty)}$ and C_{max} after single-dose administration and of $AUC_{\tau,ss}$ and $C_{max,ss}$ after multiple-dose administration of LCM – healthy subjects.

Note: The figure shows data for healthy subjects who received solid oral dosage forms of LCM (ie, capsules used early in development or tablets) and no other comedication. The linear regression was done based on the arithmetic means from the individual trials.

2.2.8.3 How do the PK parameters change with time following chronic dosing?

The terminal half-life of the unchanged drug is approximately 13 hours and is not altered by multiple dosing (see Section 2.2.9.4), different doses, or by different routes of administration

(oral or iv). Thus, steady-state of PK was in general reached after Day 3 following a twice daily dosing.

Following twice-daily dosing, the plasma concentration increases with an accumulation factor of approximately 2.3, which is illustrated in Figure 2.2.8.2.1 for C_{max} and $C_{max,ss}$, and is consistent with what is estimated from its apparent half-life of 13 hours assuming one-compartment model.

2.2.8.4 What are single dose and multiple dose PK parameters of SPM 12809?

ADME study showed that O-desmethyl metabolite, SPM 12809 is the major human metabolite of LCM which is systemically available (Section 2.2.9). This metabolite has no known pharmacological activity. Monitoring SPM 12809 levels could help understand the change in metabolism under various circumstances, e.g., renal or hepatic impairment.

After single-dose administration of lacosamide, the maximum plasma concentration of SPM 12809 occurs approximately 12 hours after dosing (range: 8-24 hours). Data from Study SP657 are shown in Table 2.2.8.4.1. At steady state, T_{max} of SPM 12809 is shorter than after single dosing, with the maximum plasma concentration at steady state occurring between 1.8 and 4 hours after dosing (range: 0.5-12 hours). Data from Study SP661 are shown in Table 2.2.8.4.2.

The terminal half-life of SPM 12809 is between approximately 15 and 23 hours and is not altered by different doses or by multiple dosing.

SPM 12809 represents approximately 10% of the parent compound in plasma (Table 2.2.8.4.3).

Table 2.2.8.4.1. Plasma PK parameters (geometric mean and CV [%]) of lacosamide and SPM 12809 after single oral administration of 200mg lacosamide as tablets — (Study SP567). b(4)

Parameter (unit)	Lacosamide Tablet (N=16)	Metabolite SPM 12809 Tablet (N=16)
$AUC_{(0-tz)}$ (µg/mL*h)	84.51 (22.2)	9.145 (50.5)
C_{max} (µg/mL)	5.263 (19.8)	0.2465 (55.7)
$A_{e(0-48)}$[a] (mg)	77.58±12.85	51.43±21.44
$t_{max,ss}$[b] (h)	1.0 (0.5-1.5)	12.0 (8-24)
$t_{1/2}$ (h)	12.48 (19.1)	20.57 (27.6)

b(4)

Table 2.2.8.4.2. Steady-state pharmacokinetic parameters of SPM 12809 in healthy subjects following 200 mg LCM twice daily dosing (Study SP661).

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)

Table 2.2.8.4.3. Ratio of SPM 12809 and LCM in plasma after repeated oral administration of 200mg LCM twice daily at steady state – SP640, SP660, and SP661.

Trial (no. of subjects)	Parameter (unit)	Statistic	LCM	SPM 12809	Ratio "SPM 12809/ LCM" (%)[d]
SP640[a] (N=57)	$AUC_{(0-12)ss}$ (µg/mL*h)	Geometric mean (CV%)	100.32 (17.6)	14.08 (44.6)	14.87
	$C_{max,ss}$ (µg/mL)		10.92 (16.8)	1.28 (44.5)	12.41
SP660[b] (N=16)	$AUC_{(0-12)ss}$ (µg/mL*h)		76.69 (20.81)	11.17 (57.6)	15.43
	$C_{max,ss}$ (µg/mL)		9.22 (17.40)	0.99 (57.9)	11.38
SP661[c] (N=12)	$AUC_{(0-12)ss}$ (µg/mL*h)		94.95 (17.3)	8.35 (43.2)	9.31
	$C_{max,ss}$ (µg/mL)		11.70 (16.2)	0.81 (43.7)	7.33

CV=coefficient of variation; LCM=lacosamide
a SP640: Data from the group of subjects receiving LCM 400mg/day, ie, 200mg LCM twice daily, are shown.
b SP660: Pooled data from Groups 1 and 2 for the treatment "LCM alone" are shown.
c SP661: Data from the group of White subjects are shown.
d Molecular weights of LCM and SPM 12809 have been considered (conversion factor: 250.3/236.3).

2.2.8.5 How does the PK of lacosamide in healthy volunteers compare to that in DPN patients?

In general, PK was similar in healthy subjects and DPN patients as determined from POP-PK analysis. Predose plasma concentrations of LCM in the target populations were comparable or slightly higher than those observed in healthy subjects at steady state (Table 2.2.8.5.1). Increased plasma concentrations of LCM in subjects with neuropathic pain in comparison to healthy subjects may be related to a higher age of subjects and/or a higher incidence rate of nephropathy in this subject population.

Table 2.2.8.5.1. Trough plasma concentrations of LCM at steady state in subjects with neuropathic pain, subjects with epilepsy, and healthy subjects – SP603, SP661, SP586, SP614, SP665.

Trial no.	Subject population	Dose	Time point	N	C_{trough} (µg/mL)
					Arithmetic mean±SD
SP603	Healthy subjects	200mg bid	Day 9	9[a]	5.7±0.83
SP661			Day 4	12[b]	5.6±1.1
SP586	Subjects with epilepsy		Day 15[c]	13	5.8±2.4
SP614	Subjects with neuropathic pain		End of MP[d]	39	7.7±3.0
SP665				28	5.7±2.6

a Data for Sequence Group 2 (starting with LCM prior to coadministration of carbamazepine) are shown for SP603.
b Data for the group of White subjects are shown for SP661.
c Data from the predose sample taken on Day 15 after 2-week treatment with 200mg LCM twice daily are shown for SP586.
d Data from the last visit of the Maintenance Phase are shown for the subgroup of subjects receiving 200mg LCM twice daily (Visit 9 in SP614, Visit 7 in SP665).

See PM review for detailed analysis.

2.2.8.6 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients, and what are the major causes of variability?

The inter- and intra-subject variability of PK parameters is low. Female and elderly showed higher exposure which may be due to lower body weight. Renal and hepatic impairment patients also showed higher exposure. Population PK analysis showed that exposure was lower (~20%) in patients who were coadministerd with carbamazepine, phenytoin or phenylbarbital.

See Section 2.3 and 2.4 and PM review.

2.2.9 What are the ADME characteristics of lacosamide?

2.2.9.1 What are the characteristics of drug absorption?

Following oral administration, Tmax for lacosamide was comparable across all trials in healthy subjects occurring approximately 0.5 to 4 hours after dosing.

In terms of extent of absorption, ^{14}C-ADME study (SP619) showed that ~40% of dose was eliminated as unchanged lacosamide in the urine suggesting that at least 40% was not metabolized. Absolute bioavailability of lacosamide was determined to be ~100% indicating an almost complete absorption of LCM after oral administration.

2.2.9.2 What are the characteristics of drug distribution?

After IV administration as well as after oral administration, the V_d of LCM was between approximately 40 and 60 L, indicating that LCM is distributed in the total body water.

Less than 15% of LCM is bound to plasma proteins.

2.2.9.3 What are the characteristics of drug metabolism?

In vitro incubation with human liver microsomes, hepatocytes, kidney microsomes, and plasma showed a low metabolic turnover of LCM (<4% at 4 hours). Two metabolites, SPM 12809 (desmethyl) and SPM 6912 (desacetyl) were found in trace quantities (<3%) (See Figure 2.2.9.3.1 for structures). However, a human radiolabeled ADME study (SP619) suggested that lacosamide was metabolized *in vivo*. Only 40% of unchanged LCM was recovered in urine and about 30% of the dose was recovered in urine as SPM 12809, the major metabolite (Table 2.2.9.3.1). Another 20% of dose was recovered as a polar fraction. Investigations with [^{14}C]-lacosamide labeled either at the carboxylic or at the benzylic carbon atom suggest that the polar fraction may be a desbenzylamine derivative. Small amounts of further metabolites (p-hydroxy-, O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and desacetyl-derivatives of LCM) representing 0.5% to 2% of the dose were also found in urine. In addition, an N-carbamoyl-O-ß-D-glucuronide of the desacetyl-metabolite was identified in SP619.

Table 2.2.9.3.1. Amounts of the parent compound LCM and its metabolites in pooled plasma and urine samples following single oral and iv administration (Study SP619).

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

iv=intravenous; n.d.=not determined as no peak of the substance was detected in chromatogram
Note: The sample radioactivity was assumed to be 100%.

The *in vivo* ADME data indicate that lacosamide is metabolized in human and SPM 12809 is the major metabolite. SPM 12809 is not pharmacologically active.

Other *in vivo* data showed that lacosamide is close to 100% bioavailable indicating that first-pass is not significant. It is not clear where lacosamide is metabolized.

The relative contribution of P450 isoforms in the oxidative metabolism of lacosamide is not clear. The sponsor incubated lacosamide with CYP2C19 ——— and identified two metabolites, SPM 12809 (6.27% at 24 hour and 6.88% at 48 hours) and SPM 6912 (1.65% at 24 hour and 7.68% at 48 hours). Lacosamide showed low but slightly faster turnover in CYP2C19 ——— than microsomes (92% remained at 24 hours and 91% remained at 48 hours). The data suggest that lacosamide is a CYP2C19 substrate and formation of SPM 12809 is via this pathway. The Sponsor did not study other CYP isoforms in the recombinant systems. The role of other enzymes in lacosamide metabolism is unknown. POP-PK data analysis showed a 20% decrease in exposure in the presence of cabamazepine, phenytoin or phenobarbital which may indicate an induction effect. As of note, all these three drugs are CYP3A inducers. Whether the data imply that CYP3A may be involved in metabolism of LCM remains to be determined.

b(4)

The molecular structures of LCM and the identified metabolites are shown in Figure 2.2.9.3.1.

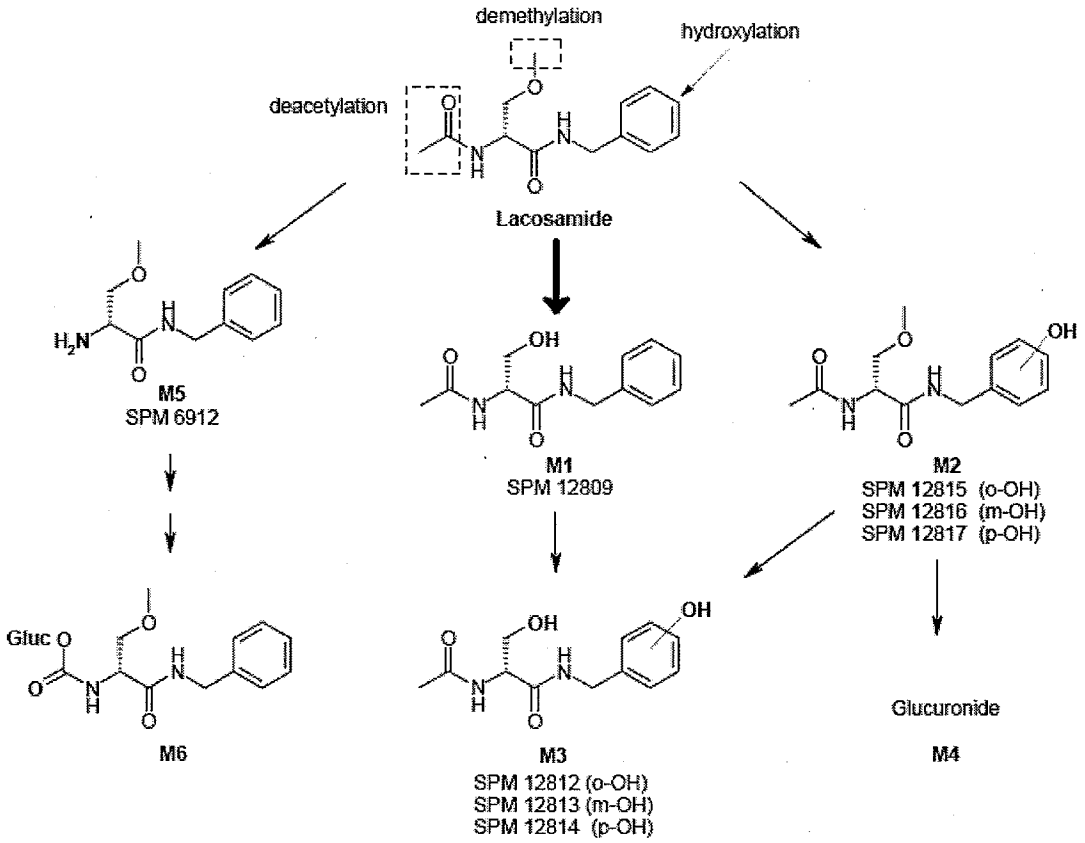


Figure 2.2.9.3.1. Observed *in vitro* and *in vivo* metabolites of lacosamide in human.

2.2.9.4 What are the characteristics of drug excretion? Does the mass balance study suggest renal or hepatic as the major route of elimination?

The terminal half-life of LCM is approximately 13 hours (see Section 2.2.8.1). After oral administration, the geometric mean of $T_{1/2}$ ranged between approximately 11 and 16 hours in healthy subjects with an interindividual variability (CV%) around 20% (Table 2.2.9.4.1).

Table 2.2.9.4.1. Terminal half-life (h) of LCM after oral administration.

Trial	n	Geom. mean (CV%)	Mean (CV%)	Median	Range
SP641	8	13.22 (17.6)	13.39 (16.9)	13.98	10.12-16.69
SP642	8	14.80 (19.73)	15.05 (19.88)	15.21	11.36-20.76
SP657	16	12.47 (19.1)	12.68 (18.0)	12.34	7.41-17.11
SP658	23	11.88 (16.3)	12.04 (17.5)	11.15	9.29-18.03
SP660	8	11.40 (22.76)	11.65 (23.1)	11.16	8.68-16.12
SP661	12	15.97 (15.9)	16.15 (15.6)	15.79	12.53-19.23

The mass balance study (SP619) suggests that the elimination of lacosamide is mainly via renal elimination. After oral and IV administration of 100mg [^{14}C]-lacosamide in healthy subjects, approximately 95% of the administered radioactivity was recovered in urine and less than 0.5% in feces (Table 2.2.9.4.2).

Table 2.2.9.4.2. Cumulative Recovery of Radioactivity (Mean ± SD, N=5 at 168 hr post dose).

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

* Mean included results calculated from data less than 30 dpm above background.

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

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

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The Sponsor evaluated the effect of the following intrinsic factors on lacosamide exposure at 80 mg dose in healthy subjects: age, gender, race, renal impairment, and hepatic impairment. As described below (Section 2.3.2), all these factors affected lacosamide exposure. In severe renal impairment patients and moderately hepatic impairment patients, AUC increased approximately 50-60% compared to healthy subjects. Because of increased adverse events observed in 600 mg daily dose vs. 400 mg daily dose, the highest daily dose in normal patients is recommended to be 400 mg. Accordingly, the highest doses in severe renal impairment patients, ESRD patients, or moderate hepatic patents should be kept at — mg/day, i.e. — of the highest doses in patients who have normal renal or hepatic function. b(4)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Age and Gender (Study SP620)

Study SP620 compared PK parameters in healthy young male, elderly male and elderly female subjects following 100 mg single dose and 100 mg bid multiple doses. Young female subjects were not studied. All subjects were Caucasians.

$AUC_{(0-\infty)}$ or $AUC_{\tau,ss}$, C_{max}, and A_e were higher in elderly male and female subjects compared with young male subjects (Table 2.3.2.1). 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 (Table 2.3.2.2). 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.

Table 2.3.2.1. Primary PK parameters of LCM following single and multiple administrations of LCM in healthy elderly male, elderly female, and young male subjects – SP620.

Parameter (unit)	Statistic	100mg single dose			100mg bid multiple dose		
		EHM	EHF	YHM	EHM	EHF	YHM
		N=12	N=12	N=12	N=11[a]	N=12	N=12
$AUC_{(0-\infty)}$ (µg/mL*h)	Geometric mean (CV%)	55.22 (24.0)[b]	60.46 (14.4)	40.76 (15.3)	n.d.	n.d.	n.d.
$AUC_{\tau,ss}$ (µg/mL*h)		n.d.	n.d.	n.d.	54.68 (23.0)	61.94 (14.0)	41.25 (13.6)
C_{max} (µg/mL)		2.77 (22.4)	3.40 (19.0)	2.16 (24.1)	6.20 (20.0)	7.36 (12.0)	4.82 (10.1)
$t_{1/2}$ (h)		16.6 (22.4)[b]	13.10 (16.6)	14.12 (22.5)	16.69 (21.5)	13.84 (21.6)	14.23 (11.0)
$A_{e(0-24)}$ (mg)	Arithmetic mean±SD	20.95 ±6.22	24.15 ±9.34	17.71 ±6.63	50.49 ±13.59	56.10 ±27.07	46.05 ±10.53

bid=bis in die (twice daily); CV=coefficient of variation; EHF=elderly healthy female; EHM=elderly healthy male; n.d.=not determined; SD=standard deviation; YHM=young healthy male

a One of the 12 elderly male subjects receiving LCM dropped out after the 72-hour sampling so that PK data are available for the SD treatment, but not for the MD treatment.

b $AUC_{(0-\infty)}$ was not calculated in 1 subject because the elimination rate constant could not be determined (N=11).

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Table 2.3.1.2. ANOVA results for age and gender group comparisons of PK parameters at steady state –SP620.

Parameter	EHM/YHM	EHF/EHM	EHF/YHM
	Ratio (90% confidence interval)		
$AUC_{\tau,ss}$	1.33 (1.18, 1.50)	1.13 (1.00, 1.28)	1.50 (1.33, 1.69)
$C_{max,ss}$	1.29 (1.16, 1.43)	1.19 (1.07, 1.31)	1.53 (1.38, 1.69)

ANOVA=analysis of variance; EHF=elderly healthy female; EHM=elderly healthy male; PK=pharmacokinetic; YHM=young healthy male

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.

Age and sex do not influence exposure in patients with partial seizure based on population PK analyses results. See PM review.

2.3.2.2 Pediatric Patients

The pharmacokinetic profile of lacosamide in pediatric patients has not been established. The Sponsor requested a deferral for initiating the pediatric development program for lacosamide (SPM 927[illegible] b(4)

2.3.2.3 Race (Study SP661)

Study SP661 evaluated the pharmacokinetics of LCM in subjects from 3 different ethnic groups (white, black and Asian) following multiple-dose administration of 200mg LCM twice daily for 3.5 days.

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%) (Table 2.3.2.3.1). 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 (Table 2.3.2.3.2).

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 (Table 2.3.2.3.3). This difference is not considered clinically relevant because the exposure of SPM 12809 is lower in Blacks and Asians compared with White subjects and SPM 12809 has no known pharmacological activity.

Table 2.3.2.3.1. Pharmacokinetic parameters of LCM and SPM 12809 after administration of 200mg LCM at steady state in Asian, Black, and White subjects – SP661

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

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

Table 2.3.2.3.2. 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)

Table 2.3.2.3.3. 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)

No dose adjustment is needed based on race.

2.3.2.4 Renal impairment (Study SP641)

Dose reduction in renal impairment patients needs to be considered.

In Study SP641, a single dose of 100 mg lacosamide was administered to patients with normal renal function, or mild, moderate, or severe renal impairment. Renal function was classified based on estimated creatinine clearance according to the FDA 1998 renal guidance. In addition, PK of lacosamide was studied in a separate group of patients with endstage renal disease (ESRD) who are on hemodialysis. Data showed that the systemic exposure of lacosamide (AUC) increased with increasing degree of renal impairment (Table 2.3.2.4.1 and Figure 2.3.2.4.1). Mean AUC increased 27%, 23%, and 59% in subjects with mild, moderate, and severe renal impairment compared with healthy subjects, respectively (Table 2.3.2.4.2). 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 2.3.2.4.1 and Figure 2.3.2.4.1).

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 2.3.2.4.1).

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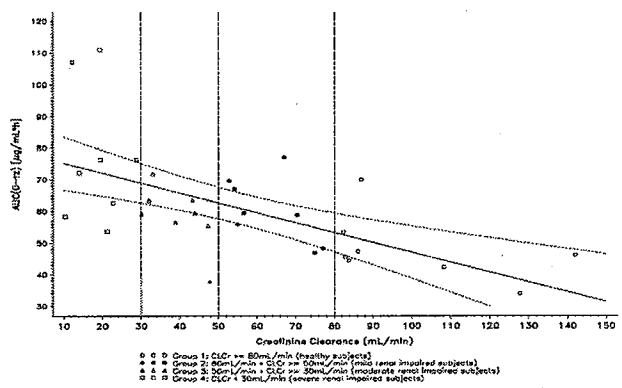
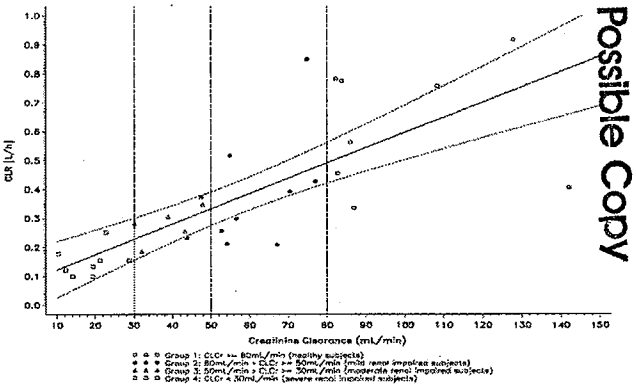


CL_{Cr}=creatinine clearance; PKS=Pharmacokinetic Set
Note: The solid line represents the regression line and the dashed line represents the 95% confidence interval.

AUC



CL_{Cr}=creatinine clearance; PKS=Pharmacokinetic Set
Note: The solid line represents the regression line and the dashed line represents the 95% confidence interval.

CL_R

Figure 2.3.2.4.1. Plot of relationship of $AUC_{(0\text{-}tz)}$ (left) and CL_R (right) of lacosamide and CL_{Cr} in healthy subjects and subjects with mild to severe renal impairment.

Table 2.3.2.4.1. Pharmacokinetic parameters of lacosamide in healthy subjects compared with subjects with mild to severe renal impairment.

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

Table 2.3.2.4.2. ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for lacosamide.

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

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

The plasma concentrations of the metabolite, SPM 12809, also increased with increasing degree of renal impairment (Table 2.3.2.4.3). The increases were more profound than lacosamide. AUC increased 4-fold in patients with severe renal impairment compared to normal renal function subjects (Table 2.3.2.4.4).

Table 2.3.2.4.3. 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.

Table 2.3.2.4.4. ANOVA results for ratios "Group X / Group 1" (with X=2, 3, or 4) for SPM 12809.

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

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

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

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 2.3.2.4.5).

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

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

Table 2.3.2.4.5. Pharmacokinetic parameters of lacosamide after Treatments A and B in subjects with end-stage renal disease, requiring dialysis.

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

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

2.3.2.5 Hepatic Impairment (Study SP642)

PK of lacosamide has not been studied in patients with mild or severe hepatic impairment. Dose reduction in moderate hepatic impairment patients needs to be considered.

In Study SP642, multiple doses of lacosamide (100 mg twice daily) were administered to patients with normal and moderate hepatic impairment (Child-Pugh Classification B). Plasma concentrations of lacosamide were approximately 50-60% higher in the subjects with moderate hepatic impairment compared to subjects with normal hepatic function (Tables 2.3.2.5.1 and 2.3.2.5.2). Half-life was prolonged and the amount of lacosamide excreted into urine within 0-12 hours after administration was reduced by approximately 20-30% in the subjects with hepatic impairment. The t_{max} was comparable between the 2 groups. Plasma concentrations of the main metabolite of lacosamide, SPM 12809, were approximately 40-50% lower in subjects with hepatic impairment compared to healthy subjects (Tables 2.3.2.5.1).

The data indicate that hepatic metabolism is involved in the metabolism of lacosamide.

Table 2.3.2.5.1. 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)

Table 2.3.2.5.2. Summary of analysis of variance of log-transformed pharmacokinetic parameters for lacosamide and SPM 12809 at steady state (Day 5) for the comparison "Moderate Impairment"/"Normal".

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

Study SP641 showed that renal impairment has an effect on lacosamide PK. In this study, 3 subjects in the moderate hepatic impairment group were classified as severe renal impairment based on the "calculated CL_{Cr}" via 24-hour urine sampling. A wide range of calculated creatinine clearances was observed in this trial (36-196mL/min at steady state). The Sponsor concluded that the PK data may be confounded by the renal function. 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).

Figure 2.3.2.5.1 below shows the relationship between $AUC_{(0-12)ss,norm}$ 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 $AUC_{(0-12)ss,norm}$ of lacosamide in a subset of subjects (~3) with hepatic impairment.

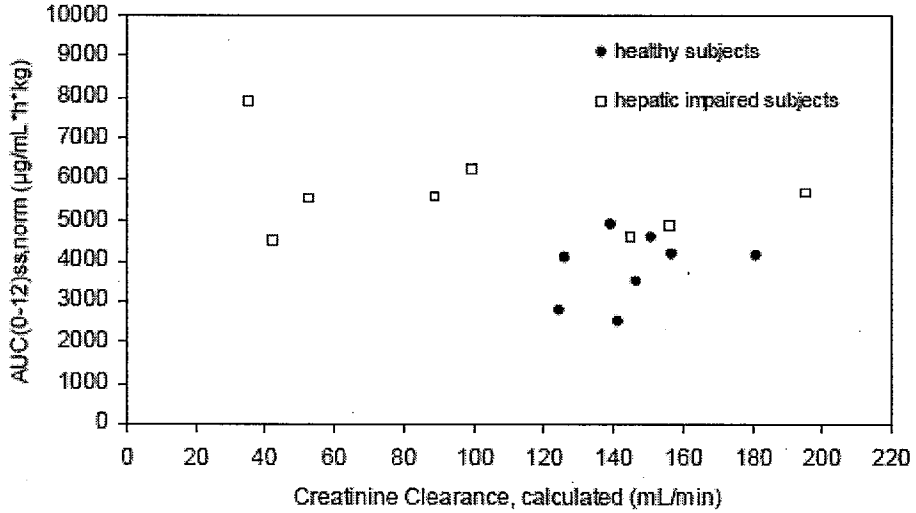


Figure 2.3.2.5.1. Relationship between $AUC_{(0-12)ss,norm}$ of lacosamide and calculated creatinine clearance at steady state (Day 5).

Additional analysis conducted by this Reviewer indicated that 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 moderate hepatic impairment patients was still 50% higher than subjects with normal hepatic function (Table 2.3.2.5.3). Based on the data, similar to recommendation for patients with severe renal impairment, the highest doses in moderate hepatic impairment patients should be reduced to — of the highest doses recommended in patients who have normal hepatic function. b(4)

Table 2.3.2.5.3. AUC and Cmax comparison between Group 1 and Group 2 stratified by renal function based on "measured CLcr".

	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% ↑

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

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

2.3.2.6 Poor and extensive CYP2C19 metabolizers (SP643)

In vitro data suggested that CYP2C19 is involved in metabolism of lacosamide to form SPM 12809. Study SP643 compared the pharmacokinetics and bioavailability of LCM when given as iv solution or as oral tablet to 4 healthy Caucasian poor metabolizers (CYP2C19-genotyped) compared with 8 healthy Caucasian extensive metabolizers. PMs were homozygous for nonfunctional alleles and EMs were either heterozygous or homozygous for wild-type alleles. Data suggested that plasma concentrations of lacosamide were comparable (not more than 10% difference) between PMs and EMs, and there were noticeable differences (75-80% difference) between PMs and EMs with respect to AUCs of the metabolite SPM 12809 (Table 2.3.6.1). See Dr. Tandon's review for additional details.

Table 2.3.2.6.1. AUC(0-tz) after oral dosing [h*µg/mL] and ratio PM/EM.

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

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The Sponsor evaluated the effects of drug-drug interactions and food on lacosamide exposure. Food effect is described in Section 2.5.5. The drug-drug interactions are described in the following Section 2.4.2.

2.4.2 Drug-drug interaction

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

Available *in vitro* data suggested that lacosamide is a CYP2C19 substrate and inhibitor. The Sponsor conducted a drug interaction study with a CYP2C19 substrate and inhibitor, omeprazole (SP863) to study the drug interaction potential (see Section 2.4.2.6.1.1).

2.4.2.2 Is lacosamide a substrate of CYP enzymes? Is metabolism influenced by genetics?

In vitro data suggested limited metabolism of lacosamide and that SPM 12809 is its major metabolite. CYP2C19 was involved in SPM 12809 formation. CYP2C19 is a polymorphic enzyme. The Sponsor conducted a PK study (SP643) in CYP2C19 EMs and PMs. See Section 2.3.2.6 and Dr. Tandon's review for additional details regarding Study SP643.

Whether lacosamide is a substrate for CYP1A2, 2B6, 2C8, 2C9, 2D6, or 3A4 is unknown.

POP-PK results showed that lacosamide exposure decreased ~20% in the presence of carbamazepine, phenytoin, or Phenobarbital (see PM review). Carbamazepine, phenytoin, and phenobarbital are CYP3A inducers. The data may suggest that CYP3A is probably involved in lacosamide metabolism.

2.4.2.3 Is lacosamide an inhibitor and/or inducer of CYP enzymes?

I/IC_{50} values of lacosamide for CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, 3A5 were estimated to be <0.1 indicating a remote possibility of *in vivo* inhibition of these enzymes. I/IC_{50} value for CYP2C19 was > 0.1 and sponsor conducted an *in vivo* study with omeprazole (a CYP2C19 substrate) to quantify the interaction.

Induction potential on CYP 1A2, 2B6, 2C9, 2C19, and 3A4 was studied with human hepatocytes. LCM did not show induction for these CYPs at therapeutic relavent concetrations.

In the drug interaction study with omeprazole, effect of multiple doses of lacosamide was studied (Study SP863). Results suggested on inhibition effect of lacosamide on omeprazole.

2.4.2.4 Is lacosamide a substrate or an inhibitor of P-glycoprotein transport process?

Lacosamide is not a P-gp substrate or inhibitor based on results in Caco-2 cells.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

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

2.4.2.6 What are the in vivo drug-drug interaction studies for lacosamide?

The potential for drug interactions was evaluated in eight *in vivo* clinical pharmacology studies which incorporated an evaluation of the relevant *in vitro* DDI results (omeprazole), drugs that can be expected to be coadministered with lacosamide (digoxin, metformin, oral contraceptive, cabamazepine, and valproic acid).

Potential for lacosamide to affect other drugs	**Potential for other drugs to affect lacosamide**
Digoxin, Oral contraceptive, Omeprazole, Metformin, Cabamazepine, Valproic Acid,	Omeprazole, Metformin, Cabamazepine, Valproic Acid

Cabamazepine and valproic acid interaction studies were mainly for the epilepsy indication and were reviewed by Dr. Tandon.

2.4.2.6.1 Individual DDI Study Result

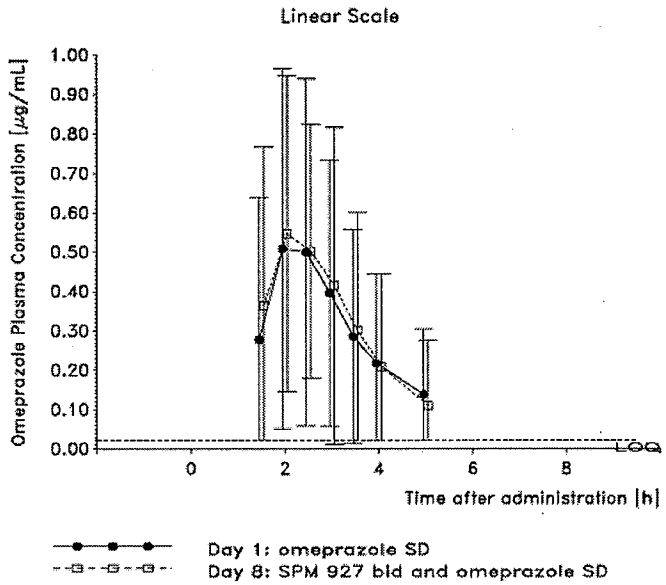
2.4.2.6.1.1 Omeprazole (SP863)
Study SP863 assessed potential PK interaction of LCM with a known substrate and inhibitor of CYP2C19 (omeprazole). Possible influence of 300 mg LCM twice daily multiple-dose treatment on the pharmacokinetics of 40 mg omeprazole single-dose treatment (Treatment A) and the possible influence of 40 mg omeprazole once daily multiple-dose treatment on the pharmacokinetics of 300mg LCM single-dose treatment (Treatment B) in healthy male White subjects were studied.

Effect on omeprazole
Multiple doses of lacosamide had no effect on omeprazole PK. The 90% CIs for $AUC_{(0\text{-}tz)}$ and C_{max} of omeprazole were contained within the acceptance range of (0.8, 1.25) (Table

2.4.2.6.1.1.1 and Figure 2.4.2.6.1.1.1), indicating that LCM does not alter the activity of CYP2C19 (no inhibition or induction).

Table 2.4.2.6.1.1.1. Summary of analysis of variance for primary PK parameters of omeprazole.

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



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

Figure 2.4.2.6.1.1.1. Mean plasma concentrations of omeprazole after administration alone and at steady state of lacosamide (N=34).

Effect of omeprazole

Pharmacokinetic parameters of LCM and SPM 12809 after single-dose administration of LCM alone and following multiple doses of omeprazole are shown in the following figure and table.

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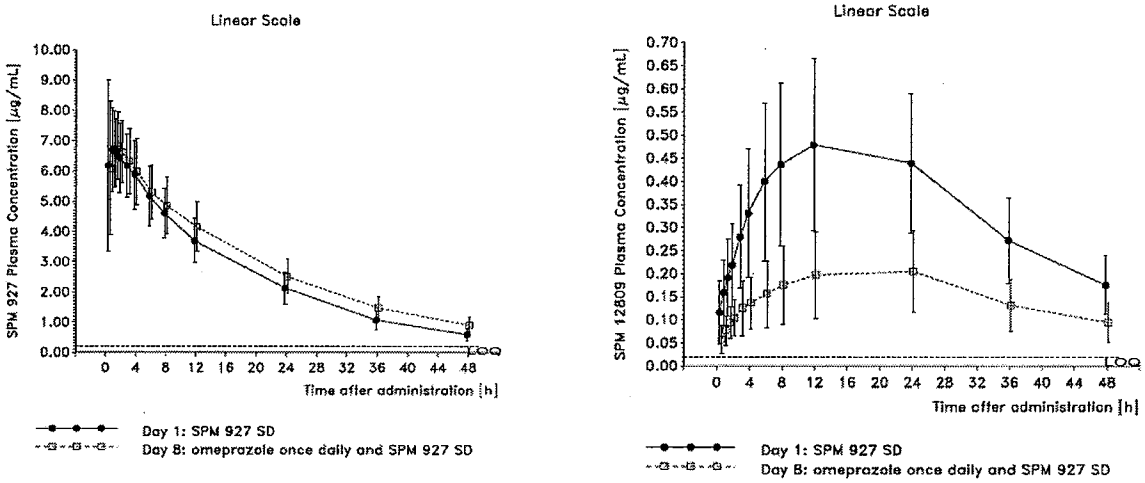


LOQ=lower limit of quantification (1.16µg/mL)

a. Lacosamide **b. SPM 12809**

Figure 2.4.2.6.1.1.2. Mean plasma concentrations of lacosamide (a) and SPM 12809 (b) after administration alone and following multiple doses of omeprazole (N=34).

Table 2.4.2.6.1.1.2. Pharmacokinetic parameters of lacosamide and SPM 12809 after administration of a single dose of 300mg lacosamide alone and following multiple doses of omeprazole.

Parameter (unit)	Statistic	Lacosamide		SPM 12809	
		Lacosamide (N=34)	Omeprazole + lacosamide (N=34)	Lacosamide (N=34)	Omeprazole + lacosamide (N=34)
$AUC_{(0-tz)}$ (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)
$AUC_{(0-\infty)}$ (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

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

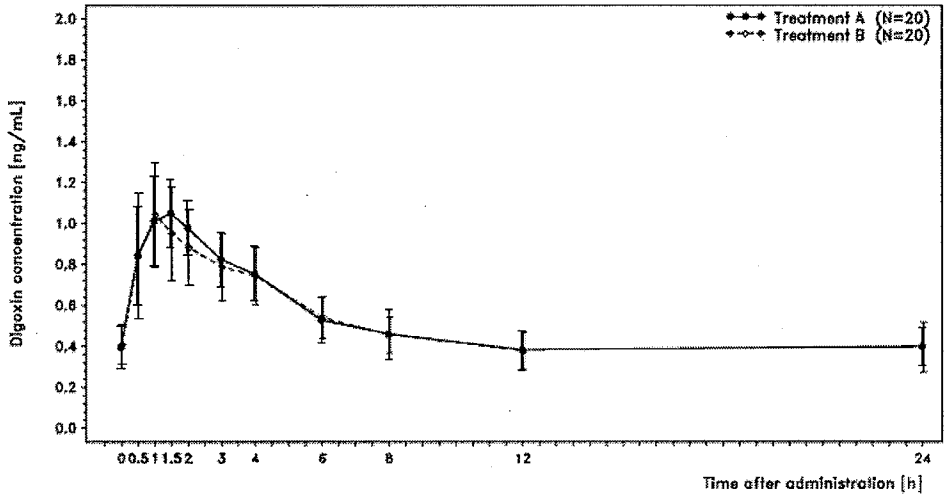
Table 2.4.2.6.1.1.3. Summary of analysis of variance for primary PK parameters of lacosamide.

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)

2.4.2.6.1.2 Digoxin (SP644)

Effect on digoxin

Results from Study SP644 suggested that coadministration of multiple doses of LCM (200 mg BID) did not alter the rate or extent of absorption of digoxin.



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

Figure 2.4.2.6.1.2.1. Mean serum concentrations of digoxin at steady state (Day 11/21) with and without co-administration of lacosamide (linear scale).

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Table 2.4.2.6.1.2.1. ANOVA results for the ratio "Treatment A / Treatment B" for digoxin.

Parameter	Point estimate	90% confidence interval
$AUC_{(0\text{-}24)ss}$	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

Effect of digoxin

Comparing lacosamide PK data to historical lacosamide PK data did not show that digoxin had an effect on lacosamide PK (Table 2.4.2.6.1.2.2).

Table 2.4.2.6.1.2.2. Pharmacokinetic parameters of LCM at steady state with and without coadministration of digoxin – SP644, SP660, SP661, and SP602.

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.

2.4.2.6.1.3 Metformin (SP660)

Drug interaction between lacosamide (200 mg BID) and metformin (500 mg TID) were studied in Study SP660 under steady-state for both.

Effect on metformin

The effect of lacosamide on metformin PK showed different trend for Group 1 (started with lacosamide on Day 1) and Group 2 (start with metformin on Day 1): Group 1 showed decreased exposure and Group 2 showed increased exposure of metformin in the presence of lacosamide (Table 2.4.2.6.1.31.). 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 reason is unknown. Pharmacodynamics of metformin was not studied. Although the 90% CIs for metformin AUC and Cmax were outside the generally accepted bioequivalence range (Table 2.4.2.6.1.3), the magnitude of changes (either increase or decrease) in metformin exposure is not considered to be clinically relevant.

Table 2.4.2.6.1.3.1. Pharmacokinetic parameters of metformin – by group and treatment.

Parameter (unit)	Group	Metformin	
		alone (N=8)	+lacosamide (N=8)
		Geometric mean (CV %)	
$AUC_{\tau,ss}$	Group 1	4595 (17.81)	3986 (21.36)
(µg/mL*h)	Group 2	3641 (20.40)	4347 (19.27)
$C_{max,ss}$	Group 1	1026 (22.12)	900.5 (24.44)
(µg/mL)	Group 2	802.8 (25.80)	941.3 (20.80)
$A_{e(0-6)}$ [a]	Group 1	168.8±45.77	189.4±83.82
(mg)	Group 2	144.9±50.84	165.0±49.5
$t_{max,ss}$ [b]	Group 1	3.0 (1.5-3)	2.5 (1.5-4)
(h)	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 2.4.2.6.1.3.2. 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)

Effect of metformin

The pharmacokinetics of LCM at steady state were comparable with and without coadministration of metformin as shown in Tables 2.4.2.6.1.3.3 and 2.4.2.6.1.3.4.

Table 2.4.2.6.1.3.3. 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 $AUC_{(0-tz)}$ 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 2.4.2.6.1.3.4. ANOVA results for primary pharmacokinetic parameters of lacosamide– by group and treatment.

Parameter	Group	Number of subjects	Ratio "lacosamide+metformin"/"lacosamide"	
			Estimate	90% confidence interval
$AUC_{\tau,ss}$	Group 1	N=8	1.0964	(1.062, 1.132)
	Group 2	N=8	1.0280	(0.996, 1.061)
$C_{max,ss}$	Group 1	N=8	1.1427	(1.044, 1.250)
	Group 2	N=8	1.0228	(0.935, 1.119)

ANOVA=analysis of variance
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.

2.4.2.6.1.4 Oral contraceptive (SP599)

Effect on oral contraceptive (Microgynon®, containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel).

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 2.4.2.6.1.4.1. 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. Because of increased exposure, there is little risk for loss of contraceptive efficacy. The 20% increase in ethinylestradiol Cmax should not pose a safety concern.

Table 2.4.2.6.1.4.1. 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)

The primary PD variable was the serum progesterone concentration on Day 21 of Cycle 3 (coadministered with lacosamide). All serum progesterone concentrations in Cycle 2 (without

LCM) as well as Cycle 3 (with LCM) were <5.1 nmol/L, which was taken as evidence of a successful suppression of ovulation.

Effect of oral contraceptive
Across study comparision showed that exposure of lacosamide (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. Because the metabolism of lacosamide is not completely understood, whether there is a potential interaction mechanism between oral contraceptives and lacosamide remains unclear.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Has adequate data been provided to support biowaiver for in vivo BE studies based on BCS classification?

The BCS committee determined that lacosamide drug substance meets the requirements of a highly soluble and highly permeable drug substance (BCS class 1) according to BCS guidance. Solubility data in various pH media indicate that lacosamide meets the BCS guidance definition for a highly soluble drug (see Section 2.1.1).

High permeability is proven by data from a mass balance study with radiolabelled lacosamide (SP619) indicating an absorption of approximately 95% of lacosamide after oral administration. Two comparative bioavailability studies (SP645 and SP658) show an absolute bioavailability of approximately 100%. In addition, an in vitro permeation study across a monolayer of epithelial cells (Caco-2 monolayer) using propranolol as highly permeable reference standard showed a clearly higher apparent permeability coefficient of lacosamide compared to propranolol. Thus, high permeability of the drug substance has been confirmed.

Refer to ONDQA review by Dr. Shiromani for detail review of the data.

2.5.2 What is formulation (quantitative composition) of the to-be-marketed lacosamide tablets?

Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets are different colored, oval. —— tablets of different size and are compositionally proportional formulations (Table 2.5.1.1). Consequently, the size and weight increase with dosage strength. The tablets are debossed with "SP" on one side and the tablet strength ("50", "100", "150", "200", "250", "300") on the other side. b(4)

Table 2.5.1.1. Quantitative composition per film-coated tablet.

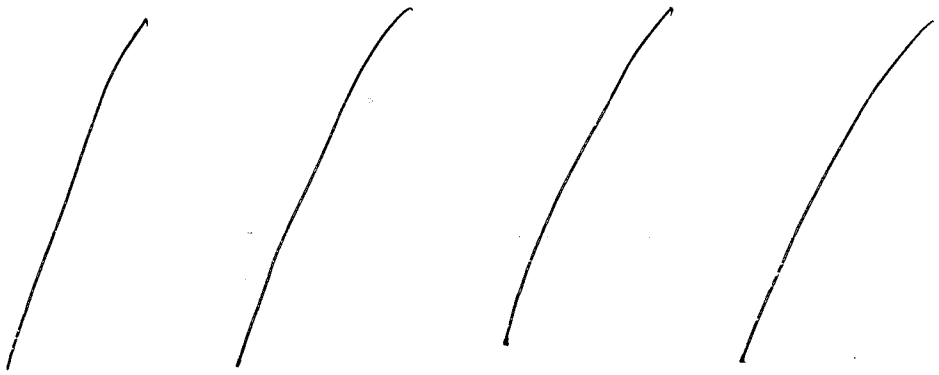
Component	Reference to standard	Function	50 mg pinkish [mg]	100 mg dark yellow [mg]	150 mg salmon [mg]	200 mg blue [mg]	250 mg [mg]	300 mg [mg]
Lacosamide	In-house	Active ingredient	50.00	100.00	150.00	200.00	250.00	300.00
Cellulose, microcrystalline	USP-NF							
Crospovidone	USP-NF							
Magnesium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

b(4)

Table 2.5.1.2 shows the quantitative composition of the different assigned to each tablet strength.

b(4)

Table 2.5.1.2. Quantitative composition of [redacted]



b(4)

2.5.3 What formulations were used in PK and clinical trials? Is the proposed to-be-marketed formulation bioequivalent to the formulations used in the pivotal PK and clinical trials?

Three major immediate-release dosage formulations were used in PK and clinical trials: hand-filled capsules with pure drug substance, capsules filled with powder blend, and the film-coated tablets. The to-be-marketed formulation is slightly different from the film-coated tablets used in clinical trials and has never been used in any clinical studies.

Table 2.5.3.1 provides an overview on the use of the different formulations in clinical trials.

Despite the differences in composition between capsules and tablets used in clinical trials and the commercial tablet formulation, the release characteristics of these immediate release solid dosage forms remained essentially the same. In addition, the excipients included in the formulations are well established and no interaction with the pharmacokinetics of the active substance is expected.

Both capsule formulations as well as the tablet formulations for clinical trials and for market launch are characterized by similar rapid dissolution *in vitro*. Since capsules were only used in some of the Phase 1 trials, the Phase 2 trials SP586 and SP598 initiated by the previous sponsor and SP611, no extensive dissolution testing at different pH-values was performed. With regard to tablets used in clinical trials since the beginning of 2001, a detailed comparison with the commercial formulation was performed.

Table 2.5.3.1. Formulations used in clinical trials.

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

Trial code	Aim of trial	Dose	Formulation
SP614	Phase 2 (diabetic neuropathy)	50 mg/100 mg	Film-coated tablets (clinical trial formulation)
SP647	Phase 2 (neuropathic pain)	50 mg/100mg	
SP655	Phase 2 (postherpetic neuralgia)	25 mg/50 mg/100 mg	
SP665	Phase 2 (diabetic neuropathy)	50 mg	
SP690	Phase 2 (postherpetic neuralgia)	50 mg/100 mg	
SP742	Phase 2 (diabetic neuropathy)	50 mg/100 mg	
SP743	Phase 2 (diabetic neuropathy)	50 mg/100 mg	
SP745	Phase 3 (diabetic neuropathy)	50 mg/100 mg	
SP746	Phase 3 (diabetic neuropathy)	50 mg/100 mg	
SP768	Phase 3 (diabetic neuropathy)	50 mg/100 mg	
SP830	Phase 3 (diabetic neuropathy)	50 mg/100 mg	
SP746 subtrial	Phase 3 (diabetic neuropathy)	50 mg/100 mg	

The Sponsor requested biowaiver for *in vivo* bioequivalence studies comparing the tablet used in clinical development and the capsules used in early development with the commercial tablet formulation. Because all formulations are immediate-release oral dosage forms with high solubility and high permeability (Class 1 drug according to the BCS) (Section 2.5.1), and are rapidly dissolving, the biowaiver for BE studies could be granted. Formulations changes are not expected to alter the bioavailability characteristics of lacosamide tablets. Refer to ONDQA review for dissolution assessment.

2.5.4 Do the to-be-marketed tablets demonstrate dosage form equivalence?

No study was conducted. However, because all dose strength tablets are proportional in composition and lacosamide has linear PK, the tablets are likely to be dosage form equivalent.

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made regarding administration in relation to meals?

Study SP600 is a food effect study that evaluated a high fat meal on the PK of a single-dose 300 mg (3 X100 mg tablets). The data (Table 2.5.5.1) suggested that food had no effect on Cmax or AUC. However, median Tmax was delayed by ~0.5 hours under fed conditions.

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Table 2.5.5.1. 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

Although food effect has not been evaluated on the highest dose strength, 300 mg tablet, this is an immediate release formulation, the different strengths are compositionally proportional and coupled with the fact that lacosamide is a BCS Class 1 drug substance, food is not expected to alter PK of the 300 mg tablet. Lacomide tablets may be taken without regard to food.

2.6 ANALYTICAL

2.6.1 What active moieties were measured in the plasma and other biological fluids in the clinical pharmacology and biopharmaceutics studies?

Both lacosamide and its major metabolite, SPM 12809, were monitored in plasma and urine in most clinical pharmacology studies.

Other appropriate moieties were also monitored in drug interaction studies.

2.6.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods measured total concentrations of all the relavent moities in human plasma.

2.6.3 What bioanalytical methods are used to assess concentrations?

For the quantification of LCM and its main metabolite SPM 12809 in clinical trials, various liquid chromatography-mass spectrometry (LC-MS) methods were developed and validated using [redacted] internal standards to provide appropriate accuracies and robustness. A complete list of analytical methods and their use in Clinical Pharmacology studies is provided in Table 2.6.3.1. b(4)

Similar sample preparation methods were used. Later methods were developed to quantify LCM and SPM 12809 simultanously in human plasma or urine. LCM or SPM 12809 along with internal standard were extracted from human plasma with ——— The corresponding method for detecting LCM or SPM 12809 in human urine used diluted urine for direct injections into the LC/MS/MS system. b(4)

A number of additional smaller analytical investigations was performed to show that coadministration of another drug did not compromise the validity of the assays (631-02; 633-02; 665-02).

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

In addition to assays related to LCM, assays to determine concentrations of ethinylestradiol (lab-da142) and levonorgestrel (lab-fx034; lab-fx034-a1), valproic acid (pc27528-2), carbamazepine (lab-ba233; — ba233-a1; — ba233-a2; — ba233-a3), digoxin (606-03; 607-03; lx014; lx014-a1), metformin (ikp031-04-05.mn), and omeprazole (ikp040-05-05-so) in plasma and urine were validated to analyze samples from PK interaction trials. For Phase 2 trial SP667 in the indication partial-onset seizures, assays to determine concentrations of carbamazepine, carbamazepine-10,11-epoxide, gabapentin, lamotrigine, felbamate, levetiracetam, 10-hydroxy oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproic aid in plasma were validated (m2003-39). b(4)

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Table 2.6.3.1. Analytical Methods for LCM and SPM 12809.

Study No.	Validation report no.	Type of assay	Matrix	Analytes	LOQ (µg/mL)[a] Linear Range	Long-term Stability at ≤-15°C
SP835 b(4)	—)584-haav-hp	LC-MS/MS	human plasma Li Heparin	LCM	1 ng/mL 1-1000 ng/mL	47 days in sodlum heparin human plasma; 336 days in potassium EDTA human plasma
	—0584-haav-hu	LC-MS/MS	human urine	LCM	0.01 0.01-10	24 days
SP587 b(4)	—-ka215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) 0.1-20 (plasma) 5 (urine) 5-500 (urine)	>6 days (plasma) >7 days (urine)
SP836 b(4)	— 0584-haav-hp	LC-MS/MS	human plasma Li Heparin	LCM	1 ng/mL 1-1000 ng/mL	See above
	— 0584-haav-hu	LC-MS/MS	human urine	LCM	0.01 0.01-10	See above
SP588 b(4)	.— ka215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) 0.1-20 (plasma) 5 (urine) 5-500 (urine)	See above
SP834 b(4)	— 0584-haav-hp	LC-MS/MS	human plasma Li Heparin	LCM	1ng/mL	See above
	—0584-haav-hu	LC-MS/MS	human urine	LCM	0.01	See above

Study No.	Validation report no.	Type of assay	Matrix	Analytes	LOQ (µg/mL)[a] Linear Range	Long-term Stability at ≤-15°C
SP641	ba583-03	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 10 ng/mL 10-10000 ng/mL SPM 12809: 10 ng/mL 10-5000 ng/mL	> 15 months (BA 558-02)
	585-02	LC-MS	human urine	LCM / SPM 12809	Both: 0.2 0.2-200	> 11 months
SP642 b(4)	— la279-1	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 0.1 0.1-20 SPM 12809: 0.02 0.02-4	>1048 days
	— la279-2	LC-MS/MS	human urine	LCM / SPM 12809	LCM: 5 5-500 SPM 12809: 1 1-100	> 14 days

SP643 b(4)	— la279-1	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 0.1 0.1-20 SPM 12809: 0.02 0.02-4	See above
	— la279-2	LC-MS/MS	human urine	LCM / SPM 12809	LCM: 5 5-500 SPM 12809: 1 1-100	See above
SP620 b(4)	— la279-1	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 0.1 0.1-20 SPM 12809: 0.02 0.02-4	See above
	— la279-2	LC-MS/MS	human urine	LCM / SPM 12809	LCM: 5 5-500 SPM 12809: 1 1-100	See above
SP661	ba583-03	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 10 ng/mL 10-10000 ng/mL SPM 12809: 10 ng/mL 10-5000 ng/mL	See above
	585-02	LC-MS	human urine	LCM / SPM 12809	Both: 0.2 0.2-200	See above

Study No.	**Validation report no.**	**Type of assay**	**Matrix**	**Analytes**	**LOQ (µg/mL)[a] Linear Range**	**Long-term Stability at ≤-15°C**
SP644 b(4)	ba583-03	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 10 ng/mL 10-10000 ng/mL SPM 12809: 10 ng/mL 10-5000 ng/mL	See above
	613-02	LC-MS/MS	human plasma	LCM / SPM 12809	Both: 0.01 0.01-10	> 15 months (BA 558-02)
	585-02	LC-MS	human urine	LCM / SPM 12809	Both: 0.2 0.2-200	See above
SP660	613-02	LC-MS/MS	human plasma	LCM / SPM 12809	Both: 0.01 0.01-10	See above
	585-02	LC-MS	human urine	LCM / SPM 12809	Both: 0.2 0.2-200	See above
SP863	ikp094/04-05-he	LC-MS	human plasma	LCM / SPM 12809	LCM: 0.1 0.1- 20 SPM 12809: 0.02 0.02-4.4	
		LC-MS	human urine	LCM / SPM 12809	LCM: 5.29 5.29- 506 SPM 12809: 1.14 1.14- 109	

SP599 b(4)	—ka215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) 0.1-20 (plasma) 5 (urine) 5-500 (urine)	See above
SP601	pc27528-1	LC-MS/MS	human plasma	LCM	0.1 0.1-20	
SP602	pc27528-1	LC-MS/MS	human plasma	LCM	0.1 0.1-20	
SP b(4)	— ka215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) 0.1-20 (plasma) 5 (urine) 5-500 (urine)	See above
SP618 b(4)	— ka215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) 0.1-20 (plasma) 5 (urine) 5-500 (urine)	See above

Study No.	**Validation eport no.**	**Type of assay**	**Matrix**	**Analytes**	**LOQ (µg/mL)[a]**	**Long-term Stability at ≤-15°C**
SP657	ikp094/04-05-he	LC-MS	human plasma	LCM / SPM 12809	0.1 (LCM) / 0.02 (SPM 12809)	
SP b(4)	ba583-03	LC-MS/MS	human plasma	LCM / SPM 12809	LCM: 10 ng/mL 10-10000 ng/mL SPM 12809: 10 ng/mL 10-5000 ng/mL	See above
SP645 b(4)	pc27528-1	LC-MS/MS	human plasma	LCM	0.1	
SP600	— .a215	LC-MS/MS	human plasma / human urine	LCM	0.1 (plasma) / 5 (urine)	See above
b(4) 40	ikp094/04-05-he	LC-MS	human plasma	LCM / SPM 12809	0.1 (LCM) / 0.02 (SPM 12809)	See above

LC=liquid chromatography; LCM=lacosamide;
Li=lithium; LOQ=lower limit of quantification; MS=mass spectrometry; PM=poor metabolizer
[a] The lower limit of quantification is given in µg/mL unless otherwise specified.

52 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2 Individual Study Reviews

4.2.1 In Vitro Metabolism/Transport Studies and In Vivo ADME

4.2.1.1 In Vitro Metabolism/Transport Study Review for Lacosamide

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4.2.1.1.1 In vitro metabolism of lacosamide

NOTE: Molar lacosamide (LCM) concentrations from *in vitro* studies were based on the molecular weight of LCM of 250.3. A LCM concentration of 1 mM equals 250 µg/mL. In clinical trials with LCM doses of 200 to 600 mg/day, plasma concentrations of LCM ranged from approximately 5 to 20 µg/mL (corresponding to 20 to 80 µM).

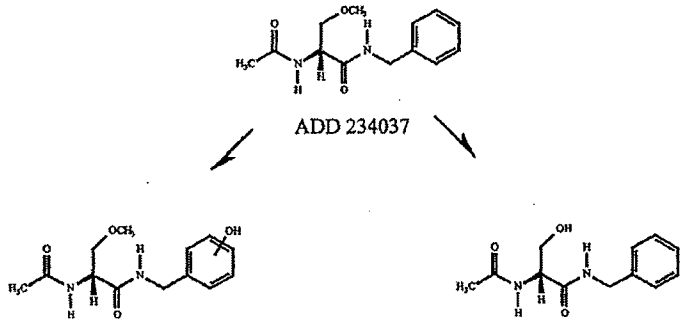
Liver Microsomes

Study 9818851 – *In vitro* metabolism of ADD 234037 (LCM) using liver microsomes from rat, dog, monkey and human

Method: ADD 234037 (100 nmol) was incubated in the standard microsomal assay at 37°C, sampled at 15, 30, and 60 minutes and analyzed by LC-MS.

Results: In vitro studies demonstrated that LCM undergoes minor oxidation to two metabolites with the site(s) of modification either at the methoxy or phenolic moietes (to form the phenolic and desmethyl metabolites) of the molecule with no apparent species differences in rat, dog and monkey but no metabolism in human. The most probable metabolites are shown in Figure 1.

Figure 1: Proposed Biotransformation of ADD 234037 (LCM)



Conclusion: LCM undergoes minor metabolism by pooled microsomes to two oxidative metabolites in rat, dog and monkey pooled microsomes. The study suggests that oxidative metabolism via cytochrome P450 plays a minor part in the hepatic clearance of LCM in humans.

Hepatocytes

Study 0699/025 – (^{14}C)-SPM 927: Metabolism in hepatocytes isolated from mouse, rat, rabbit, dog and man

Objective: To compare the metabolism of (^{14}C)-SPM 927 in suspension cultures of fresh hepatocytes isolated from the livers of male mouse, rat, dog, female rabbit and male or female human

Method:
Pilot study: Hepatocytes were incubated in duplicate in a shaking water bath at nominal test compound concentrations of 1, 10 and 100 µM (14C)-SPM 927 and sampled after 0, 1, 2, 4 and 6 hours. A set of control incubations, sampled at 6 hours, in the absence of cells, was also conducted at each concentration. The incubations were terminated by the addition of acetonitrile. The resultant suspension was mixed thoroughly and centrifuged at *ca.* 13000 rpm for 10 minutes. Supernatants were decanted into separate amber vials and stored frozen prior to analysis. Duplicate aliquots of the supernatant were taken to determine extraction recoveries by liquid scintillation counting (LSC).

Definitive study: The samples were prepared as described for the pilot study but were incubated for 2 and 4 hours with 10 µM test compound for each species and additionally for 6 and 10 hours for human donor 2. Reactions were terminated by the addition of acetonitrile, centrifuged and supernatants blown down to near dryness under nitrogen convection and reconstituted with 20 mM ammonium acetate buffer, pH 7.4/acetonitrile (98:2 *v/v*) prior to determination of recovery of radioactivity and analysis by radio-HPLC.

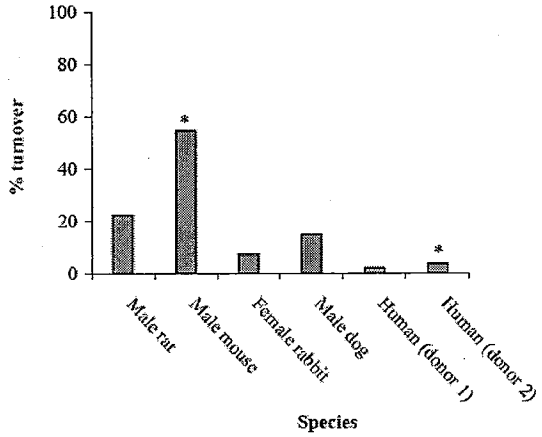
Results: The metabolism of parent compound i.e. mean metabolic turnover, at 4 hours incubation, was 54.7%, 22.2%, 7.3% and 14.8% in mouse, rat, rabbit and dog hepatocytes, respectively (Figure 1, Table 1). The rate of metabolic clearance in human hepatocytes was, under these incubation conditions, less extensive with <4% turnover following at 4 hours incubation. Qualitatively, the metabolism of (^{14}C)-SPM 927 in human hepatocytes most closely resembled that of male mouse hepatocytes. No metabolites were detected that were unique to human hepatocytes. Quantitatively, metabolism of (^{14}C)-SPM 927 in mouse and rat was more extensive while rabbit and human were notably less rapid. The order for the apparent rate of *in vitro* metabolism for each species, at 10 µM (^{14}C)-SPM 927 following both 2 and 4 hours incubation, was as follows: mouse>rat>dog>rabbit>human

LC-MS/MS analysis confirmed, with the use of reference standards, O-demethylation was common to all species while ring hydroxylation occurred in rat, rabbit and dog and deacetylation was favored in mouse and human.

Table 1:Percentage mean turnover of 10 μM (^{14}C)-SPM 927 in each species

Species	Duration of incubation (hours)	% Turnover
Male rat	4	22.2
Male mouse	4	54.7
Female rabbit	4	7.3
Male dog	4	14.8
Human (donor 1)	4	<2
Human (donor 2)	4	3.7

Figure 1: Summary of total (^{14}C)-SPM 927 turnover in hepatocytes (4 hour) in each species



Conclusions:

• Three major metabolites were detected in *in vitro* incubations of (^{14}C)-SPM 927 together with minor polar components.
• Turnover was low in dog, human and rabbit hepatocytes while metabolism was higher in mouse and rat.
• Qualitatively the metabolism of (^{14}C)-SPM 927 in hepatocytes in man only resembled mouse.
• The two major metabolites detected in rat, rabbit and dog were identified spectroscopically as SPM 12817 and SPM 12809.
• The two major metabolites detected in mouse and human were identified spectroscopically as SPM 12809 and SPM 6912.

Various In Vitro Models

Study 688 - Investigation of the metabolism of SPM 927 in different in vitro models

Objective: Identification of enzymes involved in the metabolism of [^{14}C]-SPM 927 using samples of liver and kidney microsomes obtained from the rat and human, liver and kidney

microsomal supernatant from the rat, human plasma and microsomes obtained from baculovirus infected insect cells transfected with human cytochrome P450 2C19 cDNA [redacted] b(4)

Method: The metabolism of [^{14}C]-SPM 927 was determined at 37°C using phosphate buffer (100 mM, pH 7.4) as an incubation medium in the presence of a NADPH regenerating system. The concentration of [^{14}C]-SPM 927 was 100 µM. CYP2C19 [redacted] were additionally incubated with 10 µM [^{14}C]-SPM 927. Samples were taken at different time points for up to 48 hours. The formation of metabolites was analyzed by HPLC with online radiochemical detection. To obtain information on non-cytochrome P450 enzymatic metabolism of [^{14}C]-SPM 927, incubations were performed without adding the NADPH regenerating system. Also, the influence of flavin monooxigenase (FMO) enzymes was investigated.

Results: In the in vitro rat models, a total of four significant metabolites were observed. SPM 12809 and SPM 12817 were found to account for up to 4.87 and 2.69%, respectively, of the total radioactivity in the chromatogram obtained when analyzing the rat liver microsome samples. Traces of SPM 6912 were also found in the rat liver microsomal samples. Two unknown metabolites, M1 and M2, were found to account for up to 1.64 and 1.52% in the rat liver supernatant samples. M1 was also found to account for up to 1.51% in the rat kidney microsomal supernatant. The formation of the two unknown metabolites was found to be catalyzed by non-cytochrome P450 enzymatic process in the cytosol.

Tables 1 to 5 summarize the results for the *in vitro* human models and indicate that a total of three significant metabolites were observed. SPM 12809 and SPM 6912 were found to account for up to 2.87 and 1.90%, respectively, in the microsomal samples (Table 1). In human kidney microsomes M1, M2, and M3 were found in traces after 24 hours. No further metabolites were detected. After prolongation of incubation time to 48 hours SPM 6912 was additionally found in traces. No further change in metabolite profile was detected (Table 2). After 24 hours incubation of 100 µM [^{14}C]-SPM 927 with human CYP2C19 [redacted] 2.2% of the test item was metabolized. SPM 12809 was found with 1.28% (Table 3). The unknown metabolites M2 and M3 were found in traces in samples with and without the NADPH regenerating system. No further metabolites were detected. b(4)
Additionally, the concentration of [^{14}C]-SPM 927 was reduced 10-fold to 10 µM. After 24 hours incubation with human CYP2C19 [redacted] SPM 12809 and M2 were found accounting for 6.27 and 1.65%, respectively (Table 4). M1 and M3 were found in traces in one out of two samples. After prolongation of incubation time to 48 hours only SPM 12809 and M2 were detected with 6.88 and 7.68%, respectively. No further metabolites were detected.
After 24 hours incubation of 100 µM [^{14}C]-SPM 927 in human plasma with and without NADPH regenerating system no metabolism was observed (Table 5).

Additionally, the influence of flavin monooxigenase enzymes (FMOs) in the metabolism of [14C]-SPM 927 was investigated. Therefore, the pH value was shifted to pH 9.5 to optimize the incubation conditions for FMO metabolism. After 24 hours incubation of 100 µM [^{14}C]-SPM 927 with human liver and kidney microsomes only marginal amounts of the test item were metabolized, 1.6 and 1.3%, respectively. The addition of [redacted] a detergent to inactivate membrane bound enzymes like cytochrome P450, caused only a negligible reduction in the b(4)

metabolism of [^{14}C]-SPM 927 in liver and kidney microsomes to 1.3 and 0.9%. After the addition of a combination of —— and thiourea, a specific FMO inhibitor, the metabolism of [^{14}C]-SPM 927 was further reduced to 0.9 and 0.5% in liver and kidney microsomes, respectively. b(4)

Table 1: Human liver microsomes

Sample time [h]	0	4	6	24	48
	[% total radioactivity]				
SPM 927	100.30	97.46	96.74	94.51	93.66
SPM 12809	n.d.	1.22	1.55	2.46	2.87
SPM 12812	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12813	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12817	n.d.	n.d.	n.d.	traces	traces
SPM 6912	n.d.	traces	1.05	1.40	1.90
M1	n.d.	n.d.	traces	traces	traces
M2	n.d.	traces	traces	traces	traces
M3	n.d.	traces	traces	traces	traces

n.d.: not detected; traces: >0.1 and <1.0 % total radioactivity
Data given are mean of duplicates

Table 2: Human kidney microsomes

Sample time [h]	0	4	6	24	48
	[% total radioactivity]				
SPM 927	100.23	99.78	99.58	98.34	98.37
SPM 12809	n.d.	n.d.	n.d.	traces	n.d.
SPM 12812	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12813	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12817	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 6912	n.d.	n.d.	n.d.	n.d.	traces
M1	n.d.	traces	traces	traces	traces
M2	n.d.	traces	traces	traces	traces
M3	n.d.	n.d.	n.d.	traces	traces

n.d.: not detected; traces: >0.1 and <1.0 % total radioactivity
Data given are mean of duplicates

Table 3: Human CYP2C19 [redacted] incubated with 100 µM SPM 927

100 µM [^{14}C]-SPM 927 as substrate

Sample time [h]	With NADPH regenerating system						Without NADPH
	0	0.5	1	2	4	24	24
	[% total radioactivity]						
SPM 927	100.25	99.87	99.48	99.24	98.79	98.06	98.99
SPM 12809	n.d.	traces	traces	1.00	1.24	1.28	n.d.
SPM 12812	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12813	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12817	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 6912	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M2	n.d.	traces	traces	traces	traces	traces	traces
M3	n.d.	n.d.	n.d.	n.d.	n.d.	traces	traces

n.d.: not detected; traces: >0.1 and <1.0 % total radioactivity

Data given are mean of duplicates

Table 4: Human CYP2C19 [redacted] incubated with 10 µM SPM 927

10 µM [^{14}C]-SPM 927 as substrate

Sample time [h]	0	4	6	24	48
	[% total radioactivity]				
SPM 927	100.00	92.59	92.69	92.00	90.83
SPM 12809	n.d.	6.72	6.34	6.27	6.88
SPM 12812	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12813	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12817	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 6912	n.d.	n.d.	n.d.	n.d.	n.d.
M1	n.d.	n.d.	n.d.	traces	n.d.
M2	traces	traces	traces	1.65	7.68
M3	n.d.	n.d.	n.d.	traces	n.d.

n.d.: not detected;

Data given are mean of duplicates

Table 5: Human plasma

Sample time [h]	With NADPH regenerating system						Without NADPH
	0	0.5	1	2	4	24	24
	[% total radioactivity]						
SPM 927	100.36	100.31	100.33	100.33	100.36	100.16	100.03
SPM 12809	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12812	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12813	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 12817	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
SPM 6912	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

n.d.: not detected

Data given are mean of duplicates

Conclusions:
In the in vitro rat models, a total of four significant metabolites were observed. SPM 12809 and SPM 12817 were found to account for up to 4.87 and 2.69%, respectively, of the total radioactivity in the chromatogram obtained when analyzing the rat liver microsome samples. Traces of SPM 6912 were also found in the rat liver microsomal samples. Two unknown metabolites, M1 and M2, were found to account for up to 1.64 and 1.52% in the rat liver supernatant samples. M1 was also found to account for up to 1.51% in the rat kidney microsomal supernatant. The formation of the two unknown metabolites was found to be catalyzed by non-cytochrome P450 enzymatic process in the cytosol.

In the in vitro human models, a total of three significant metabolites were observed up to 48 hours. SPM 12809 and SPM 6912 were found to account for up to 2.87 and 1.90%, respectively, in the microsomal samples. Using human CYP2C19 —— a total of two significant metabolites were observed. SPM 12809 and the unknown metabolite M2 were found to account for up to 6.88 and 7.68%, respectively. b(4)

The results for human CYP2C19 microsomes indicated that CYP2C19 is able to catalyze the metabolism of LCM.

4.2.1.1.2 In vitro induction and inhibition of CYP isoforms

CYP Induction

Study BA 555-02 – Investigation of the cytochrome P450 1A2 and 3A4 induction potential SPM 927 in cryopreserved human hepatocytes

Method: Human hepatocytes of 2 donors were incubated with 50 and 500 µM of SPM 927. Positive controls (β-naphthoflavone, dexamethasone, rifampin) and solvent/vehicle controls (DMSO, acetonitrile) were included. Cytoxicity of SPM 927 was tested and was not observed at the applied concentrations. The CYP activity after the induction phase with SPM 927 and incubation with the CYP test substrates 7-ethoxy-resorufin and testosterone were analyzed in the cell culture supernatant by determination of the CYP1A2 specific metabolite resorufin and CYP3A4 specific metabolite 6β -hydroxytestoterone. The n-fold induction in relation to the solvent/vehicle control was expressed as induction factor "IF". The cut-off for positive induction was IF ≥ 1.5.

Results: Tables 1 and 2 summarize the results of the study. No CYP1A2 activity induction was observed at both concentrations of SPM 927. A slight induction of CYP3A4 was observed in one out 2 donors at 500 µM of SPM 927 using acetonitrile as solvent but the induction is less than that observed with dexamethasone, thus implying a very weak in vitro induction potential for 500 µM of SPM 927.

Table 1: CYP1A2 induction

Sequence	Donor/Lot #	Induction Factor			
		Compound			
		SC	bNF	SPM927[1] (50 µM)	SPM927[2] (500 µM)
1	082	1.0	2.2	0.5	0.4
	130	1.0	17.8	0.6	0.8
2	082	1.0	1.4	0.8	0.9
	130	1.0	20.9	0.6	0.6

SC: solvent control, sequence 1: 1% DMSO, sequence 2: 1% acetonitrile
bNF: β-naphthoflavone
[1] 0.1%, v/v of the respective solvent
[2] 1%, v/v of the respective solvent

Table 2: CYP3A4 induction

Sequence	Donor/Lot #	Induction Factor				
		Compound				
		SC	Dex	Rif	SPM927[1] (50 µM)	SPM927[2] (500 µM)
1	082	1.0	1.5	2.3	---	1.4
	130	1.0	1.1	3.3	---	1.2
2	082	1.0	1.2	3.2	1.0	1.0
	130	1.0	3.0	11.0	1.2	1.7

SC: solvent control, sequence 1: 1% DMSO, sequence 2: 1% acetonitrile
Dex: dexamethasone, Rif: rifampicin
---: experimental error, calculation not reasonable
[1] 0.1%, v/v of the respective solvent
[2] 1%, v/v of the respective solvent

Conclusion: SPM 927 displayed no CYP1A2 induction activity at 50 and 500 µM, and CYP3A4 induction activity at 50 µM. A slight induction of CYP3A4 was observed in one out 2 donors at 500 µM of SPM 927 using acetonitrile as vehicle.

Study 732: Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes

Method: Cryopreserved hepatocytes were obtained from male and female human donors. After plating hepatocytes were allowed to recover for 24 hours before incubating with lacosamide (50 and 500 µM) or control inducers for 72 hours. Following incubation, the induction potential was evaluated by quantifying the following cytochrome P450 isoform specific enzymatic activities: 7-ethoxyresorufin O-deethylation (CYP1A2), phenacetin O-deethylation (CYP1A2) (S)-mephenytoin N-demethylation (CYP2B6), (S)-warfarin 7-hydroxylation (CYP2C9), (S)-mephenytoin 4-hydroxylation (CYP2C19), and testosterone 6β-hydroxylation (CYP3A4).

Results: The change in cytochrome P450 enzymatic activities following treatment is summarized in Table 1. The cut-off for a positive induction was a higher than 200% change in

enzymatic activity of treated versus non-treated hepatocytes (control). Down regulation was considered significant when the enzymatic activity of the treated hepatocytes was below 50% of that obtained for the non-treated hepatocytes.

Results obtained from cryopreserved hepatocytes for control inducer substances show that CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4 enzymatic activities were inducible. CYP2E1 as described in the study plan was not inducible and is not reported.
Human hepatocytes treated at therapeutic concentrations did not induce any of the tested cytochrome P450 enzymes. In one donor the 10-fold higher lacosamide concentration resulted in enzyme activities of CYP3A4, that were three times higher than the solvent treated group, but less than 0.2 times lower than the positive induced control group.

Table 1: Change in CPY450 activities following the treatments.

	Donor	Substrate (concentration)	Control inducer		Lacosamide % of control		
			Compound (concentration)	% of control	50 µM	500 µM	
CYP1A2	—	7-ethoxyresorufin	Omeprazole	633	96.8	102	b(6)
	—	(7.5 µM)	(100 µM)	536	86.0	91.4	
	417			258	93.1	93.7	
	—	Phenacetin	Omeprazole	2988	92.9	104	
	—	(100 µM)	(100 µM)	1835	90.1	98.0	b(6)
	417			822	100	115	
CYP2B6		(S)-mephenytoin	Phenobarbital	490	93.3	88.5	
	—	(100 µM)	(200 µM)	536	89.0	148	b(6)
	417			220	93.4	129	
CYP2C9	—	(S)-warfarin	Rifampicin	333	110	180	
	417	(10 µM)	(20 µM)	219	112	110	
CYP2C19	—	(S)-mephenytoin	Rifampicin	215	98.0	74.6	
	—	(100 µM)	(20 µM)	216	73.6	61.4	
CYP3A4	—	Testosterone	Rifampicin	2018	103	131	b(6)
	—	(250 µM)	(20 µM)	1921	161	323	
	417			> 934	n.a.	n.a.	

Conclusions: Results obtained for the control inducer substances show that the CYP1A2, CYP2B6, and CYP3A4 enzymatic activities were inducible in all donors, CYP2C9 and CYP2C19 in two out of three donors.
Except in one case the results obtained following incubation with lacosamide show no change in the enzymatic activity of all CYPs tested. Human hepatocytes treated at therapeutic concentrations (50 µmol/L or 12.5 µg/mL and 500 µmol/L or 125 µg/mL) did not show a relevant induction of any of the tested CYP isoforms (1A2, 2B6, 2C9, 2C19, and 3A4). In one donor the 10-fold higher lacosamide concentration resulted in enzyme activities of CYP3A4, that were three times higher than the solvent treated group, but less than 0.2 times lower than the positive induced control group.

CYP Inhibition

Study M1999-057 – An investigation of the potential of LCM to inhibit cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4

Objective: To determine the potential for LCM to inhibit human liver cytochrome P450 (CYP) enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4.

Method: The following probe substrates were used to investigate the inhibitory potential of the test articles on the respective enzymes: phenacetin for CYP1A2, coumarin for CYP2A6, tolbutamide for CYP2C9, S-mephenytoin for CYP2C19, dextromethophan for CYP2D6, chlorzoxazone for CYP 2E1 and testosterone for CYP3A4. The activity of each enzyme was determined in human hepatocytes in the presence and absence of each test article and positive control inhibitor. Significant inhibition is defined as ≥ 50%.

Results: Tables 1 to 5 summarize the results of the study that with the exception of CYP2C19, LCM showed no potential to inhibit CYP450 activity in the in vitro human hepatocytes system.

Reviewer's Note: The plasma concentrations of LCM ranged from approximately 5 to 20 µg/mL (corresponding to 20 to 80 µM) with LCM doses of 200 to 600mg/day. If assume IC_{50} of 100 µM based on the 59.9% inhibition of CYP2C19 at 100 µM, I/IC_{50} would be >0.1, indicating potential for interaction with a CYP2C19 substrate. The Sponsor conducted a drug interaction study with omperazole (a CYP2C19 substrate) and found no interaction (Section 4.2.5.1).

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Table 1: Metabolic activities of phenacetin (CYP1A2) in human hepatocytes incubated with harkoseride or positive control inhibitor

Control/ Test Article	Conc (uM)	Phenacetin Acetaminophen Production (pmol/mg protein/min)	Phenacetin Percent Inhibition
NC	NA	7.2 ± 1.3	0.0 ± 18.4
FUR	10	0.0	100.0
Harkoseride	100	6.8 ± 0.4	6.1 ± 6.4

Values are the mean ± standard deviation of N = 3 replicates.
Abbreviations: Conc, concentration; NC, negative control; NA, not applicable; FUR, furafylline.

Table 2: Metabolic activities of coumarin (CYP2A6) in human hepatocytes incubated with harkoseride or positive control inhibitor

Control/ Test Article	Conc (uM)	Coumarin 7-HC Production (pmol/mg protein/min)	Coumarin Percent Inhibition	Coumarin 7-HCG Production (pmol/mg protein/min)	Coumarin Percent Inhibition
NC	NA	5.2 ± 0.2	0.0 ± 4.6	2.9 ± 0.8	0.0 ± 27.6
TRN	250	0.0	100.0	0.0	100.0
Harkoseride	100	5.6 ± 0.5	-9.1 ± 8.9	3.6 ± 1.5	-23.0 ± 40.5

Values are the mean ± standard deviation of N = 3 replicates.
Abbreviations: Conc, concentration; ACN, acetaminophen; 7-HC, 7-hydroxycoumarin; 7-HCG, 7-hydroxycoumarin glucuronide; NC, negative control; NA, not applicable; TRN, tranylcypromine; FUR, furafylline.

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ON ORIGINAL

Table 3: Metabolic activities of tolbutamide (CYP2C9) and *S*-mephenytoin (CYP2C19) in human hepatocytes incubated with harkoseride or positive control inhibitor

Control/ Test Article	Conc (uM)	Tolbutamide 4-OH TB Production* (pmol/mg protein/min)	Tolbutamide Percent Inhibition	*S*-mephenytoin 4-OH ME Production (pmol/mg protein/min)	*S*-mephenytoin Percent Inhibition
NC	NA	3.3 ± 0.2	0.0 ± 6.7	2.7 ± 0.5	0.0 ± 18.4
SULF	1	0.0	100.0	NA	NA
OME	10	NA	NA	0.0	100.0
Harkoseride	100	3.8 ± 0.6	-14.1 ± 16.5	1.1 ± 0.1	59.9 ± 6.2

Values are the mean ± standard deviation of N = 3 replicates.
Abbreviations: Conc. concentration; 4-OH TB, 4-hydroxytolbutamide; 4-OH ME, 4-hydroxy-mephenytoin; NC, negative control; NA, not applicable; SULF, sulfaphenazole; OME, omeprazole.
*Presented in terms of parent disappearance due to poor chromatographic resolution.

Table 4: Metabolic activities of dextromethorphan (CYP2D6) and chlorzoxazone (CYP2E1) in human hepatocytes incubated with harkoseride or positive control inhibitor

Control/ Test Article	Conc (uM)	Dextromethorphan DEX Production (pmol/mg protein/min)	Dextromethorphan Percent Inhibition	Chlorzoxazone 6-OH CZX Production (pmol/mg protein/min)	Chlorzoxazone Percent Inhibition
NC	NA	6.6 ± 0.2	0.0 ± 2.7	59.2 ± 1.2	0.0 ± 2.0
4-MP	100	NA	NA	0.0	100.0
QUIN	1	0.0	100.0	NA	NA
Harkoseride	100	7.0 ± 0.4	-5.4 ± 5.2	60.3 ± 0.3	-1.9 ± 0.5

Values are the mean ± standard deviation of N = 3 replicates.
Abbreviations: Conc. concentration; DEX, dextromethorphan; 6-OH CZX, 6-hydroxychlorzoxazone; NC, negative control; NA, not applicable; 4-MP, 4-methylpyrazole; QUIN, quinidine.

Table 5: Metabolic activities of testosterone (CYP3A4) in human hepatocytes incubated with harkoseride or positive control inhibitor

Control/ Test Article	Conc (uM)	Testosterone 6β-Hydroxytestosterone Production (pmol/mg protein/min)	Percent Inhibition
NC	NA	1.1 ± 0.3	0.0 ± 27.5
Ketoconazole	1	0.0	100.0
Harkoseride	100	1.3 ± 0.1	-16.9 ± 6.2

Values are the mean ± standard deviation of N = 3 replicates.
Abbreviations: Conc. concentration; NC. negative control; NA, not applicable.

Conclusions: With the exception of CYP2C19, LCM showed no potential to inhibit CYP450 activity in the *in vitro* human hepatocytes system.

Reviewer's Note: The Sponsor conducted a drug interaction study with omperazole (a CYP2C19 substrate) and found no interaction (Section 4.2.5.1).

Study BA 481-03 – Interaction of the compounds SPM 927 and SPM 12809 (Desmethyl-SPM 927) with Cytochrome P450 isoenzymes 1A2, 3A4, 2C9, 2C19 and 2D6

Method: SPM 927 and SPM 12809 were analyzed to detect possible interactions with the human cytochrome P450 isoenzymes 1A2. 3A4, 2C9, 2C19 and 2D6. Phenytoin was included for control purposed as it may be co-administered with SPM 927. The interaction analysis of the test compounds was performed with a fully automated microtiter plate-based competitive inhibition assay in which specific CYP-substrates are converted to fluorogenic metabolites in the presence of test compounds (competitors) or specific control inhibitors. The specifice inhibitors furafylline (CYP1A2), ketoconazole (CYP3A4), sulfaphenazole (CYP2C9), omeparazole (CYP2C19) and quinidine (CYP2D6) were included as controls.

Test compounds and the NADPH-regenerating system were pre-incubated for 10 min at 37°C. The enzymatic reaction was iniatiated by addition of CYP-enzyme/substrate mix. The reaction was terminated with a stop-reagent (80%v/v acetonitrile/0.1M tris base) after incubation at 37°C. The fluorescence intensities of the substrate-metabolite formed were measured and concentrations of metabolite product were calculated from the standard curves of of the standard metabolites.
The logIC_{50}, IC_{50} and K_i values were estimated from 8 different concentrations of the test compound (triplicates) and the control inhibitors (duplicates).

Results: There was no inhibitory interactions between SPM 927 or SPM 12809 with Cytochrome P450 isoenzymes 1A2, 3A4, 2C9, 2C19 and 2D6 (Table 1). Phenytoin is a substrate of CYP2C9 and CYP2C19 as well as an inducer of CYP3A4. The phenytoin results indicate low to moderate *in vitro* inhibition of CYP3A4, CYP2C9 and CYP2C19.

Table 1: IC_{50} and K_i values

	$LogIC_{50}$	IC_{50} [µM]	K_i [µM]
CYP1A2:			
SPM 927:	low interaction, calculation not reasonable		
(c = 400 – 0.183 µM)			
SPM 927:	no interaction detectable		
(c = 200 – 0.091 µM)			
SPM 12809:	no interaction detectable		
Phenytoin:	no interaction detectable		
Furafylline:	3.107 ± 0.034	1.280	0.533
	3.086 ± 0.014	1.220	0.508
CYP3A4:			
SPM 927:	no interaction detectable		
SPM 12809:	no interaction detectable		
Phenytoin:	5.177 ± 0.224	150.3	96.5
Ketoconazole:	1.383 ± 0.070	0.024	0.015
	1.344 ± 0.067	0.022	0.014
CYP2C9:			
SPM 927:	no interaction detectable		
SPM 12809:	no interaction detectable		
Phenytoin:	4.910 ± 0.093	81.3	41.8
Sulfaphenazole:	2.516 ± 0.035	0.328	0.169
	2.545 ± 0.034	0.351	0.181

CYP2C19:			
SPM 927:	no interaction detectable		
SPM 12809:	no interaction detectable		
Phenytoin:	4.666 ± 0.044	46.3	25.1
Omeprazole:	3.391 ± 0.050	2.459	1.333
	3.412 ± 0.062	2.581	1.399
CYP2D6:			
SPM 927:	no interaction detectable		
SPM 12809:	no interaction detectable		
Phenytoin:	no interaction detectable		
Quinidine:	1.352 ± 0.041	0.023	0.011
	1.356 ± 0.035	0.023	0.011

Conclusion: No inhibitory interactions between SPM 927 or SPM 12809 with CYP 1A2, 3A4, 2C9, 2C19 and 2D6. The phenytoin results indicate low to moderate *in vitro* inhibition of CYP3A4, CYP2C9 and CYP2C19.

Study 865 - Inhibition of the cytochrome P450 isoenzymes 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 and SPM 12809

Objective: Investigation of the in vitro inhibition of the human cytochrome P450 (CYP) isoenzymes 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 in a concentration range from 18 to 40000 µM and SPM 12809 in a concentration range from 5 to 10000 µM.

Method: The inhibitory interaction analysis was performed with fully automated microtiter plate-based fluorometric endpoint assays using cDNA-derived human CYP isoenzymes in microsomal preparations from insect cells. The CYP isoform specific inhibitors α-naphthoflavone (CYP1A1), tranylcypromine (CYP2A6, CYP2B6), quercetin (CYP2C8), sodium diethyldithiocarbamate (CYP2E1) and ketoconazole (CYP3A5) were included as controls. IC50 values were estimated.

Results: Table 1 to 3 summarize the results obtained from the study.
No inhibition of the CYP isoenzymes 2A6, 2B6, 2C8 and 2E1 by SPM 927 and SPM 12809 was detectable (Table 1 & 2).
The IC50 value for the inhibition of CYP1A1 by SPM 927 was calculated to be 47.8 mM (11950 µg/mL). The IC50 values for the inhibition of CYP3A5 by SPM 927 and SPM 12809 were calculated to be 3.31 and 6.20 mM (830 and 1460 µg/mL), respectively.
The IC50 values of the specific inhibitors α-naphthoflavone (CYP1A1), tranylcypromine

(CYP2A6, CYP2B6), quercetin (CYP2C8), sodium diethyldithiocarbamate (CYP2E1) and ketoconazole (CYP3A5) were calculated to be 0.27 µM, 0.64 µM, 9.33 µM, 1.15 µM, 3.24 µM and 0.27 µM respectively and are in good agreement with literature values (table 3).

Table 1: IC_{50} values

	Test samples (conc. range)	IC_{50}
CYP1A1	SPM 927 (40000 – 18 µM)	47.8 mM
	SPM 12809 (10000 – 5 µM)	no inhibition detectable
	α-naphthoflavone (5000 – 2 nM)	0.27 µM
CYP2A6	SPM 927 (40000 – 18 µM)	no inhibition detectable
	SPM 12809 (10000 – 5 µM)	no inhibition detectable
	TCP (25000 – 11 nM)	0.64 µM
CYP2B6	SPM 927 (40000 – 18 µM)	no inhibition detectable
	SPM 12809 (10000 – 5 µM)	no inhibition detectable
	TCP (125000 – 57 nM)	9.33 µM

Table 2: IC_{50} values

	Test samples (conc. range)	IC_{50}
CYP2C8	SPM 927 (40000 – 18 µM)	no inhibition detectable
	SPM 12809 (10000 – 5 µM)	no inhibition detectable
	Quercetin (10000 – 5 nM)	1.15 µM
CYP2E1	SPM 927 (40000 – 18 µM)	no inhibition detectable
	SPM 12809 (10000 – 5 µM)	no inhibition detectable
	DDTC (100000 – 46 nM)	3.24 µM
CYP3A5	SPM 927 (40000 – 18 µM)	3.31 mM
	SPM 12809 (10000 – 5 µM)	6.20 mM
	Ketoconazole (5000 – 2 nM)	0.27 µM

Table 3: Controls, CYP-specific inhibitors and IC_{50} values

Enzyme/substrate/specific inhibitor	IC_{50} [µM] study data	previous data in house	literature data
1A1 / CEC / α-naphthoflavone	0.27	0.38	no data
2A6 / coumarin / TCP	0.64	0.51	0.25
2B6 / EFC / TCP	9.33	7.27	5.0
2C8 / DBF / quercetin	1.15	1.29	1.5
2E1 / MFC / DDTC	3.24	2.49	4.1
3A5 / BFC / ketoconazole	0.27	0.2	0.1

Conclusion: No inhibitory interactions with CYP2A6, 2B6, 2C8, and 2E1 were detectable for LCM or SPM 12809. Although inhibition of CYP1A1 by SPM 927 and inhibition of CYP3A5 by SPM 927 and SPM 12809 was observed, results suggest that there is no risk of drug-drug interactions. The ratio of SPM 12809 over lacosamide was less than 20% in terms of Cmax in human plasma (SP640). CYP1A1 was inhibited by SPM 927 with an IC50 value of 47.8mmol/L (11950µg/mL) but not by SPM 12809. The IC50 values for the inhibition of CYP3A5 by LCM and SPM 12809 were calculated to be 3.31 and 6.20mmol/L (830 and 1460µg/mL), respectively. Again, the inhibitory concentrations markedly exceed human plasma levels of 14.5 µg/mL after oral administration of 300 mg twice daily (SP588). The calculated IC_{50} values were at least 57 fold higher than the human plasma concentrations.

The IC_{50} values calculated for the CYP-specific inhibitors α-naphthoflavone, tranylcypromine, quercetin, sodium diethyldithiocarbamate and ketoconazole showed good agreement with the values determined by the supplier and provide validity of data generated.

4.2.1.1.3 In vitro transport processes

Potential as a P-glycoprotein Substrate and Inhibitor

Study 651: Transport of SPM 927 across Caco-2 monolayer - Investigation of P-glycoprotein involvement

Objectives: To investigate the permeability of SPM 927 across Caco-2 cell monolayer, to investigate the involvement of active transport and the ability of SPM 927 to modulate the P-glycoprotein (Pgp) mediated transport of digoxin over a concentration range from 10 µM to 3 mM.

Methods:

Transport experiments

Before initiating an experiment the pH of the transport media was adjusted to pH 7.4 for the Basolateral Transport Medium (BM) and to pH 6.5 for the Apical Transport Medium (AM) and the rinse medium. Prior to use the cells were washed twice in rinse medium and equilibrated for one hour at 37°C in the incubator. In all experiments the volume in the apical chamber was 100 µL and in the basolateral chamber 600 µL. 50 µL aliquots from the apical side and 100 µL from the basolateral compartment were taken for analysis. For determination of the total dosed radioactivity 100 µL from each dosing solution were counted in duplicate.
As an internal quality control of each cell batch the monolayer integrity and the cell tightness were assessed by investigating the apparent coefficients of permeation of mannitol (passive paracellular transport) and propranolol (passive transcellular transport) in the AB direction. The functional expression of Pgp in each cell batch was controlled by measuring the bidirectional transport of vinblastine in the absence and presence of the Pgp modulator verapamil.
During the transport studies, the plates were maintained in the incubator at ca. 37°C in a humidified atmosphere of 5% CO2.

Transport of SPM 927

The transport of SPM 927 was examined in both directions, from apical to basolateral (AB) and from basolateral to apical (BA). For the study of AB transport, medium in the upper compartment was replaced by AM containing SPM 927 (apical dosing solution) in the following concentrations: c = 125 µM and c = 1 mM. For the study of BA transport, medium in the lower compartment was replaced by BM containing SPM 927 (basolateral dosing solution) at c = 125 µM and c = 1 mM.
At time points of 30, 60, 90, 120, and 150 minutes after addition of test compound, sample aliquots were removed from the receiver compartment. This volume was replaced with an equal volume of the appropriate medium. After 150 minutes an aliquot from the donor compartment was taken to compare dosed activity.
The transport of the control substances was assessed after 120 minutes in a similar manner.

Pgp involvement of SPM 927 transport

The transport of SPM 927 was investigated up to 150 minutes at two concentrations (125 µM and 1 mM) in the absence and presence of the Pgp modulator verapamil.
For the study of AB transport, medium in the upper compartment was replaced by AM containing SPM 927 (apical dosing solution). To determine the effect of verapamil on the AB transport, 100 µM verapamil was added to the apical dosing solution and to the BM.
For the study of BA transport, medium in the lower compartment was replaced by BM containing SPM 927 (basolateral dosing solution). To determine the effect of verapamil on the BA transport, 100 µM verapamil was added to the basolateral dosing solution and to the receiver chamber.
At time points of 30, 60, 90, 120, and 150 minutes after addition of test compound, an aliquot was removed from the receiver compartment. This volume was replaced with an equal volume of the appropriate medium. As a positive control, the bidirectional transport of vinblastine (Pgp substrate) in the absence and presence of verapamil (Pgp inhibitor) was tested after 120 minutes.

Modulation of radiolabeled digoxin transport by SPM 927

The transport of digoxin was examined in both directions after 240 minutes. To determine the effect of SPM 927 on the digoxin transport, SPM 927 (non radiolabeled) in different concentrations (c = 10 – 30 – 100 - 300 µM, 1 and 3 mM) was added to the dosing solution and to the medium of the appropriate receiver compartment.
For the study of AB transport, medium in the upper compartment was replaced by AM containing 5 µM radiolabeled digoxin in the absence and presence of SPM 927.
For the study of BA transport, medium in the lower compartment was replaced by BM containing 5 µM radiolabeled digoxin in the absence and presence of SPM 927.
As a positive control the transport of digoxin in the absence and presence of verapamil as Pgp inhibitor was tested.

Radioactivity was determined by liquid scintillation counting.

Results: The results obtained from the study are shown in Tables 1 to 4 and Figures and 2.
The transport of SPM 927 across the Caco-2 monolayer at 125 µM and 1 mM was found to be linear in a time dependent fashion in both the AB as well as in the BA direction (Table 1, Figure 1). Mean Papp values (apparent coefficient of permeation) for the transport of SPM 927 at 125 µM and 1 mM in the AB direction were found to be 163.9 ± 14.6 nm/s and 156.9 ± 6.8 nm/s, respectively. In the BA direction the Papp values at each concentration were determined to be 212.3 ± 23.8 nm/s and 217.7 ± 28.2 nm/s, respectively. The ratios of the BA/AB transport were found to be 1.3 and 1.4, respectively, indicating the involvement of no active efflux transporter.

The mean Papp values of SPM 927 at 125 µM and 1 mM in the presence of verapamil (a Pgp inhibitor) in the AB direction were found to be 208.6 ± 7.5 nm/s and 174.5 ± 16.2 nm/s, respectively. The mean Papp values in the presence of verapamil in the BA direction were found to be 227.9 ± 28.4 nm/s and 231.2 ± 5.6 nm/s, respectively. The ratios of BA/AB transport for SPM 927 at 125 µM and 1 mM in the presence of verapamil were determined to be 1.1 and 1.3 respectively. The absence or presence of verapamil was found to have no influence on the BA/AB transport ratios of SPM 927 and the Pgp involvement in the SPM 927 transport is excluded (Table 2).

SPM 927 at10, 30, 100, 300 µM, 1 and 3 mM was found to have no influence on the Pgp mediated transport of digoxin. The % inhibition of Pgp mediated transport of digoxin was calculated to be -9.1, 3.9, 1.9, 2.5, 18.8 and 18.9% at each concentration (Tables 3 and 4, Figure 2).

SPM 927 was no substrate for P-glycoprotein, and did not modulate the transport of digoxin at concentrations up to 3 mM.

Table 1 Cumulative transport of SPM 927 in both directions, apical to basolateral (AB) and basolateral to apical (BA).

		Cumulative transport of SPM 927 (dpm)			
		125 µM		1 mM	
Replicate	time	AB	BA	AB	BA
1	30	5430	7704	47760	59238
	60	10337	15342	84682	116869
	90	13715	21989	117983	170116
	120	18336	29493	150881	224828
	150	20619	35977	173979	274334
2	30	5130	7780	44982	72882
	60	10083	14610	84939	140447
	90	13997	20786	117454	208016
	120	17917	28380	149997	277758
	150	20554	33959	178134	334450
3	30	6069	9348	43938	76250
	60	10778	16256	83577	152455
	90	15105	23965	117610	215116
	120	18880	32103	150559	288473
	150	22074	38931	179497	344830

Table 2 Permeability coefficients (Papp) for the transport of SPM 927 in both directions, apical to basolateral (AB) and basolateral to apical (BA).

		Papp [nm/s]		AB transport			BA transport			Ratio
	Replicate	AB	BA	Mean Papp	SD	Imprecision	Mean Papp	SD	Imprecision	BA/AB
SPM 927	1	160.3	197.6	163.9	14.6	8.9	212.3	23.8	11.2	1.3
125 µM	2	151.4	199.6							
(control)	3	180.0	239.8							
+ verapamil	1	210.1	208.0	208.6	7.5	3.6	227.9	28.4	12.5	1.1
100 µM	2	215.2	260.5							
	3	200.5	215.3							
SPM 927	1	164.5	185.7	156.9	6.8	4.3	217.7	28.2	13.0	1.4
1 mM	2	154.9	228.5							
(control)	3	151.3	239.0							
+ verapamil	1	187.0	225.9	174.5	16.2	9.3	231.2	5.6	2.4	1.3
100 µM	2	180.4	237.0							
	3	156.2	230.7							

Table 3 The effect of SPM 927 on the transport of digoxin in both directions, apical to basolateral (AB) and basolateral to apical (BA).

	[^{3}H]-Digoxin transport at 240 minutes (Papp)													
	Apical to basolateral transport (AB)							Basolateral to apical transport (BA)						
SPM 927	Replicate					%	%	Replicate					%	%
[µM]	1	2	3	mean	SD	SD	control	1	2	3	mean	SD	SD	control
0				10.6	1.1	10.6	100.0				155.8	12.0	7.7	100.0
10				9.5	0.4	4.0	89.3				167.9	28.6	17.1	107.7
30				9.7	0.8	7.8	91.8				149.3	12.8	8.6	95.8
100				11.3	1.3	11.3	106.6				153.8	14.7	9.6	98.7
300				10.1	1.3	13.2	95.0				151.7	20.8	13.7	97.4
1000				11.3	1.0	8.7	106.9				129.3	23.1	17.9	83.0
3000				15.2	0.3	2.3	143.4				133.0	2.2	1.6	85.4

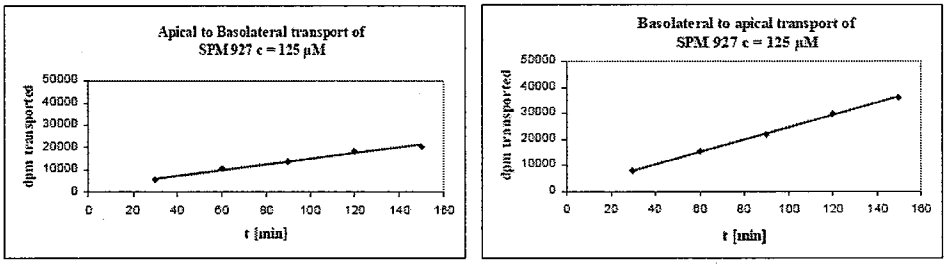
b(4)

Table 4 BA/AB ratio of the digoxin transport in the absence and presence of SPM 927 in different concentrations and percentage of inhibition.

	Mean Papp [nm/s] AB	BA	Ratio BA/AB	Percentage of inhibition
Digoxin 5 µM (control)	10.6	155.8	14.7	
+ Verapamil 100 µM	50.7	57.7	1.1	**95.2**
+ SPM 927 10 µM	9.5	167.9	17.7	**-9.1**
+ SPM 927 30 µM	9.7	149.3	15.3	**3.9**
+ SPM 927 100 µM	11.3	153.8	13.6	**1.9**
+ SPM 927 300 µM	10.1	151.7	15.1	**2.5**
+ SPM 927 1 mM	11.3	129.3	11.4	**18.8**
+ SPM 927 3 mM	15.2	133.0	8.8	**18.9**

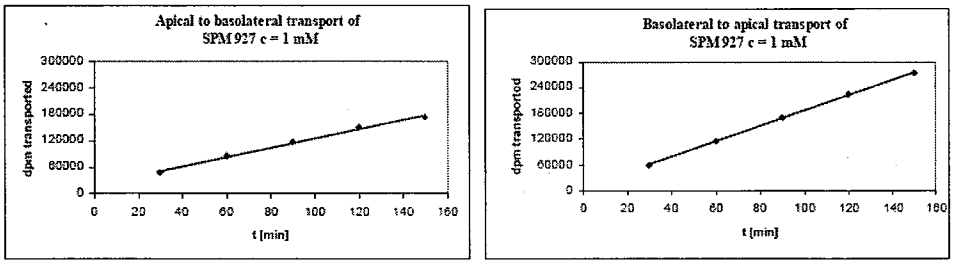
Figure 1 Cumulative transport of SPM 927 in both the AB and BA direction

a. SPM 927 c = 125 µM



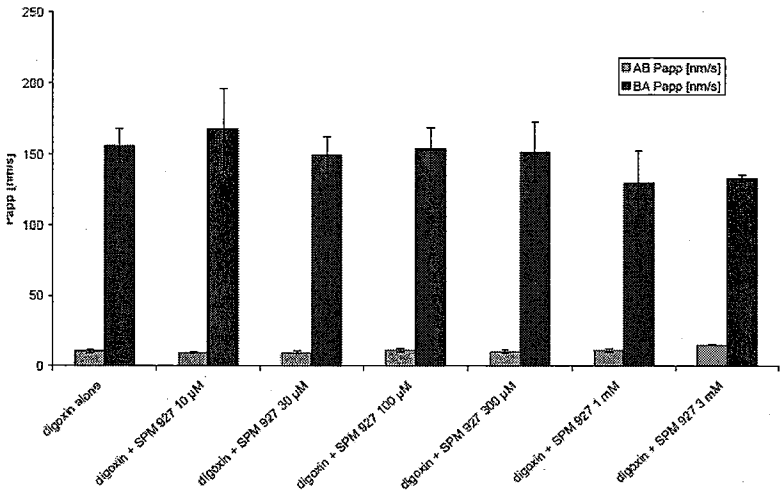
Cumulative transport data are plotted for replicate one

b. SPM 927 c = 1 mM



Cumulative transport data are plotted for replicate one

Figure 2 Bar chart to illustrate the effect of SPM 927 in different concentrations on the AB and BA transport of digoxin.



Conclusions: SPM 927 was found to permeate across the Caco-2 monolayers in a linear time-dependent fashion in the concentration range from 125 µM to 1 mM and no involvement of active efflux transporters. The absence or presence of verapamil (a P-gp inhibitor) was found to have no influence on the BA/AB transport ratios of SPM 927.

SPM 927 did not modulate the Pgp mediated transport of digoxin at concentrations up to 3mmol/L. The clinical significance of this finding in unclear, as there is no modulation of the digoxin transport in the AB direction, being the model for the drug transport from the luminal site into the blood, in vivo. Therefore, SPM 927 is no substrate for P-glycoprotein, and does not modulate the transport of digoxin at concentrations up to 3 mM.

An vivo drug interaction study with conducted with digoxin later (Study SP644) and there is no effect of lacosomide on digoxin PK, suggesting that lacosmide did not inhibit P-gp at clinical doses.

4.2.1.1.4 Plasma protein binding

Study 699/016: (^{14}C)-SPM 927: *In vitro* binding to plasma proteins in mouse, rat, dog and human

Objectives

The objectives of this study were to determine the extent of *in vitro* binding to plasma proteins and the extent of *in vitro* plasma/blood cell partitioning of (^{14}C)-SPM 927 in mouse, rat, dog and man

Method:

A) Plasma Protein Binding

The non-specific binding of (^{14}C)-SPM 927 to the —— equilibrium dialyser and the time taken to reach equilibrium was determined by dialysis of spiked phosphate buffered saline (pH 7.4) at nominal concentrations of 1.5 and 60 µg/mL. Dialysis was performed against phosphate buffered saline (pH 7.4), in duplicate, at *ca* 37°C for 0, 0.5, 1, 2, 4 and 6 hours. The *in vitro* binding of (14C)-SPM 927 to mouse, rat, dog and human plasma proteins was investigated by equilibrium dialysis, using a —— equilibrium dialyser. Samples of plasma were spiked with (^{14}C)-SPM 927 at nominal concentrations of 1.5, 4.5, 9, 15, 30 and 60 µg/mL. Duplicate portions were subjected to equilibrium dialysis against phosphate buffered saline (pH 7.4) for *ca* 4 hours. b(4)

B) Plasma/Blood Cell Partitioning

The equilibration time of (^{14}C)-SPM 927 binding to mouse, rat, dog and human red blood cells was determined following incubation in fresh whole blood of each species, at nominal concentrations of 1.5 and 60 µg/mL. Incubations were performed in duplicate for *ca* 0, 10, 30, 60 and 120 minutes at *ca* 37°C on a blood roller. Equilibration time was determined by blood:plasma ratio at each timepoint. The partitioning of (^{14}C)-SPM 927 to red blood cells of mouse, rat, dog and human blood was determined at nominal concentrations of 1.5, 4.5, 9, 15, 30 and 60 µg/mL. Duplicate portions of whole blood from each species, spiked with appropriate concentrations of (^{14}C)-SPM 927, were incubated for *ca* 60 minutes at *ca* 37°C on a blood roller.

Data Processing:

The percentage binding to plasma proteins was calculated from the equation:

$$\% \text{ binding} = \frac{\text{dpm/mL protein compartment} - \text{dpm/mL buffer compartment}}{\text{dpm/mL protein compartment}} \times 100$$

The proportion of radiolabelled material in the blood associated with the blood cells was calculated from the following expressions:

$$\text{blood:plasma ratio} = C_b/C$$

$$\text{partition coefficient} = \frac{C(1-H)}{C_b}$$

$$\% \text{ associated with red blood cells} = 100 - \text{partition coefficient}$$

where: C = plasma concentration of radioactivity

C_b = blood concentration of radioactivity

H = haematocrit as a fraction

Results:

A) Binding of (^{14}C)-SPM 927 to Plasma Proteins

The recovery of radioactivity over the entire concentration range and for all species was >84% The mean binding of (^{14}C)-SPM 927 to human plasma proteins varied between 3.8% and 8.7% over the concentration range, with an overall mean value of 6.1%. No concentration dependent effects were observed. Binding to human plasma proteins was therefore very low and non-saturable (see Table 1 below).

Table 1.

Mean *in vitro* binding of (^{14}C)-SPM 927 to male mouse, rat, dog and human plasma proteins at *ca* 37°C for 4 hours at various target concentrations

Nominal (^{14}C)-SPM 927 concentration (µg/mL)	% Protein Binding			
	Mouse	Rat	Dog	Human
1.5	4.74	4.62	20.2	5.44
4.5	4.37	6.24	18.7	6.62
9	7.18	9.65	18.2	8.73
15	7.61	1.71	17.9	3.79
30	6.81[Y]	3.05[Y]	13.0	5.52
60	6.38	5.43	11.1	6.74
Overall Mean	6.18	5.12	16.52	6.14

all values are the mean of duplicates except [Y] which is the result of a single determination

B) Plasma/Blood Cell Partitioning

The mean blood cell partitioning of (^{14}C)-SPM 927 over the entire concentration range studied was 49, 44, 47 and 54% in the mouse, rat, dog and human, respectively (Table 2).

Corresponding mean blood:plasma ratios were 1.01, 0.99, 0.87 and 0.98 (Table 3). No discernible trends in blood cell partitioning values and blood:plasma ratios were observed in mouse, rat and human over the concentration range studied.

Blood cell partitioning and blood:plasma ratios were of the same magnitude between these three species.

Table 2.

Mean *in vitro* partitioning of (^{14}C)-SPM 927 to male mouse, rat, dog and human blood cells following incubation at *ca* 37°C for 60 minutes at various target concentrations

Nominal (^{14}C)-SPM 927 concentration (µg/mL)	% Blood Cell Partitioning			
	Mouse	Rat	Dog	Human
1.5	49.37	42.91	35.90	54.82
4.5	47.05	45.53	48.45	53.29
9	49.19	43.89	47.03	53.94
15	48.43	43.94	45.28	54.77
30	47.96	46.41	51.01	54.35
60	49.17	44.10	52.06	52.55
Overall Mean	48.53	44.46	46.62	53.95

Table 3.

Mean *in vitro* blood:plasma ratio of (^{14}C)-SPM 927 following incubation at *ca* 37°C for 60 minutes with mouse, rat, dog and human blood at various target concentrations

Nominal (^{14}C)-SPM 927 concentration (µg/mL)	Blood:Plasma Ratio			
	Mouse	Rat	Dog	Human
1.5	1.027	0.963	0.718	0.996
4.5	0.982	1.010	0.893	0.964
9	1.024	0.981	0.868	0.977
15	1.009	0.981	0.841	0.995
30	0.999	1.027	0.939	0.986
60	1.025	0.984	0.959	0.949
Overall Mean	1.011	0.991	0.870	0.978

Conclusions:

- The overall mean plasma protein binding of ^{14}C-SPM 927 over the concentration range was very low at 6.2%, 5.1% and 6.1% in mouse, rat and human, respectively. No concentration dependent effects were observed.
- Mean blood cell partitioning of ^{14}C-SPM 927 was 49, 44, 47 and 54% in mouse, rat, dog and human, respectively, over the concentration range. No concentration dependent trends in blood cell partitioning were observed in humans.

Study 9827351: Ultrafiltration Using the ——— for Assessing ADD 234037 (*aka.* LCM) in Human Plasma Protein Binding b(4)

In this study, an ultrafiltration method was used to determine protein binding for LCM from ex vivo plasma samples. The selected plasma samples were obtained from Study DDS 631518/FRC 101 where healthy subjects received IV infusion of LCM. Results showed that levels of LCM in ultrafiltrate and plasma were comparable and maximum binding observed was 13% (see Table below). Therefore, plasma protein binding is <15% for LCM.

Human Plasma Protein Binding of ADD 234037 b(4)

Subject #	Ultrafiltrate Conc.	Plasma Conc.	% free	% bound
1	107		129	-29
2	99		115	-15
3	42		120	-20
[redacted]				
8	96		97	3
9	159		88	12
10	88		92	8
[redacted]				
15	121		100	0
16	129		87	13
17	147		98	2
[redacted]				
24	196		96	4
25	276		100	0
26	226		104	-4
		Average	102	-2

4.2.1.2 In Vivo ADME Study:

Study SP619: Open-Label, Randomized, Single Dose Study to Evaluate the Absorption, Metabolism, and Excretion of [^{14}C]-Labeled SPM 927 (LCM or Lacosamide) Following Oral and Intravenous Administration to 10 Healthy Male Caucasian Subjects.

Clinical Investigator: [redacted] b(4)

Study Period: July 2, 2001 to July 26, 2001

Objectives: To determine the concentrations of total radioactivity, SPM 927 and its metabolites in whole blood, plasma, urine, and feces following administration of radiolabeled SPM 927 as oral solution and solution for infusion and to describe the pharmacokinetics, the pattern of metabolites in plasma, urine, and feces, the extent of absorption, and the bioavailability.

Study Design: This was a randomized, open-label, single-dose, single-center, parallel group Phase 1 trial with 2 groups of 5 healthy male subjects. Subjects in 1 group received a single oral dose of 100 mg radiolabeled SPM 927 ([^{14}C] oral solution, Batch No. 010702). Subjects in the other group received a single iv dose of 100 mg radiolabeled SPM 927 ([^{14}C] solution for infusion, Batch No. 010702), administered over 60 minutes. Whole blood, plasma, urine, and feces were collected during a 7-day inpatient phase. The two treatments were:
Treatment A (n=5): 100 mg [^{14}C]- SPM 927 (40 µCi), given as an oral solution
Treatment B (n=5): 100 mg [^{14}C]- SPM 927 (40 µCi), given as an iv infusion over a 1 h period

Blood sampling times: 12 ml sample at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 h post dose. Also at 0.25, 0.75, and 1.25 h post iv administration.

Urine sampling times: pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, $t_{1/2}$), urine and fecal excretion ration (oral vs iv) and urine to feces ratio (to estimate the extent of absorption)

Analytical Methodologies:
Total radioactivity: Validated Liquid Scintillation Counter method; LOQ: 0.010 3 x 100 mg SPM 927 tablets as a single dose /ml
Metabolite Profiling: Radio-HPLC and LC-MS-MS

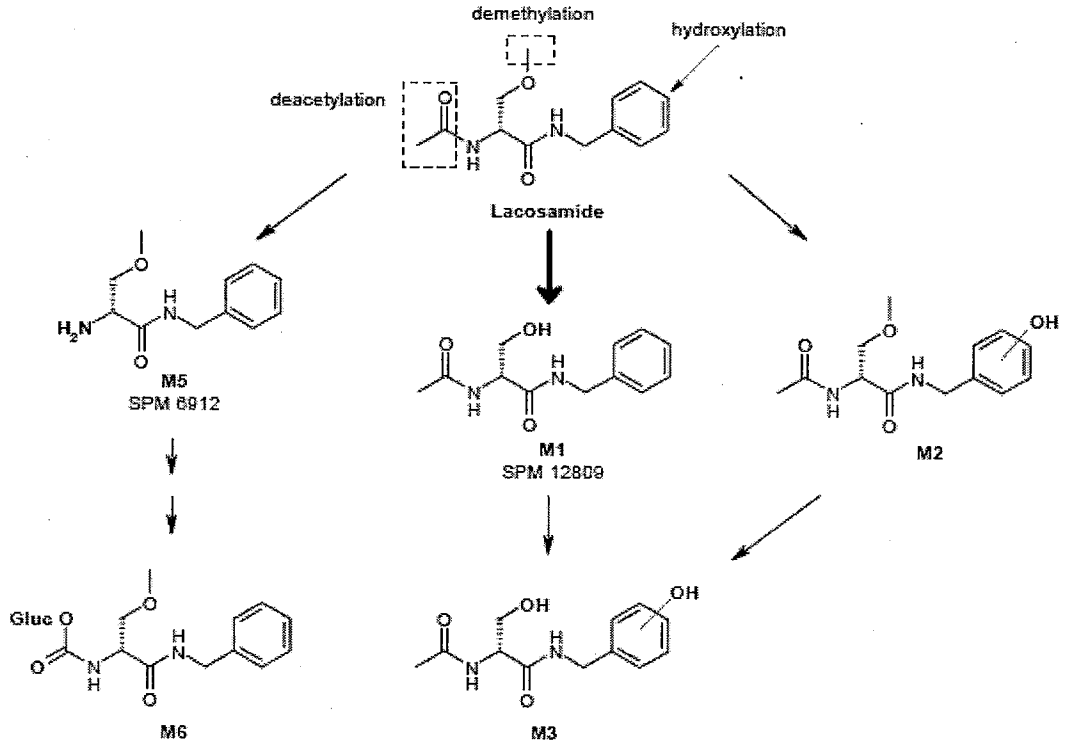
Data Analysis: PK parameters were calculated by non-compartmental using WinNonlin version 1.1.

Results:

Study Population: 10 subjects were enrolled and all completed the study. The mean age (SD) of the subjects was 40.5 years (9.0). Subjects in both treatments are comparable for age, weight and heights. All subjects were male Caucasians.

Pharmacokinetics: Refer to Figure 1 for proposed metabolic pathway of lacosamide in human.

Figure 1: Proposed metabolic pathway of lacosamide in human.



Pharmacokinetic parameters of total radioactivity following administration of 100 mg ^{14}C-SPM 927 via oral or IV route in whole blood and plasma are shown in Table 1. Mean PK profiles of total radioactivity following both treatments are shown in Figures 2. PK profiles for unchanged SPM 927 was not determined.

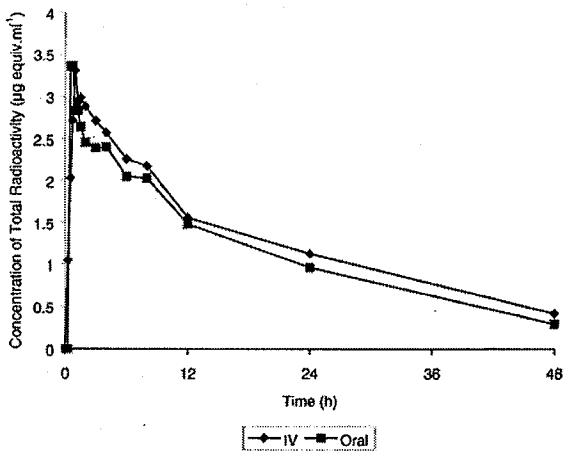
The data indicate that following oral administration of SPM 927, total radioactivity exposure was 86.7% and 83.8% of the exposure following iv administration in plasma and whole blood, respectively. The data also suggested no preferential binding of SPM 927 to red blood cells.

Table 1: Pharmacokinetic parameters of SPM 927 following a single administration of 100 mg SPM 927 as [^{14}C] oral solution or [^{14}C] solution for infusion in healthy male subjects.

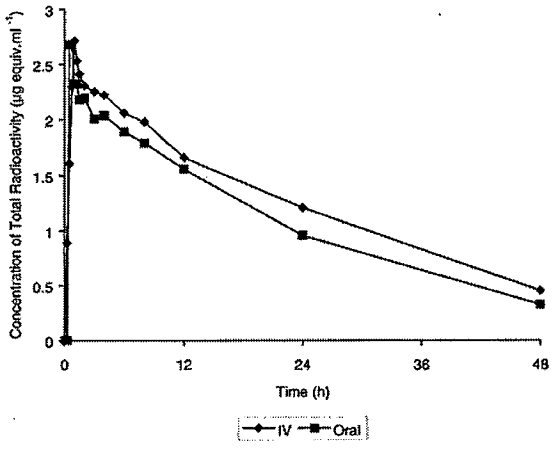
Sample	Drug formulation	N	$AUC_{(0-\infty)}$ (µg eq.h/mL)	$AUC_{(0-tz)}$ (µg eq.h/mL)	C_{max} (µg eq/mL)	$t_{1/2}$ (h)	t_{max} (h)
			Mean (standard deviation)				Median (range)
Plasma	[^{14}C] oral solution	5	62.22 (10.01)	58.59 (10.76)	3.362 (0.6083)	15.04 (3.27)	0.50 (0.50-1.00)
	[^{14}C] solution for infusion	5	71.78 (6.990)	68.46 (5.959)	3.384 (0.3269)	16.26 (2.03)	1.00 (1.00-2.00)
Whole blood	[^{14}C] oral solution	5	61.48 (10.96)	56.98 (11.52)	2.682 (0.2422)	16.03 (3.53)	0.50 (0.50-0.50)
	[^{14}C] solution for infusion	5	73.34 (7.224)	67.61 (5.961)	2.730 (0.1840)	18.01 (1.80)	1.00 (1.00-1.25)

eq=equivalent; LCM=lacosamide
$AUC_{(0-\infty)}$ = area under the concentration-time curve from zero up to infinity
$AUC_{(0-tz)}$ = area under the concentration-time curve from zero up to the last concentration
C_{max} = observed maximum plasma concentration after administration
$t_{1/2}$ = terminal half-life
t_{max} = time to reach C_{max}

Figure 2. Mean Concentration of Total Radioactivity in Plasma (a) and Whole Blood (b) Following Single Oral or Intravenous Administration of [^{14}C]-SPM 927 to Healthy Male Volunteers.



a. Plasma



b. Whole Blood

Total radioactivity was excreted primarily via the urine, with a mean of 94.2% and 96.8% of the administered dose recovered by 168 h post dose via oral and IV administration, respectively

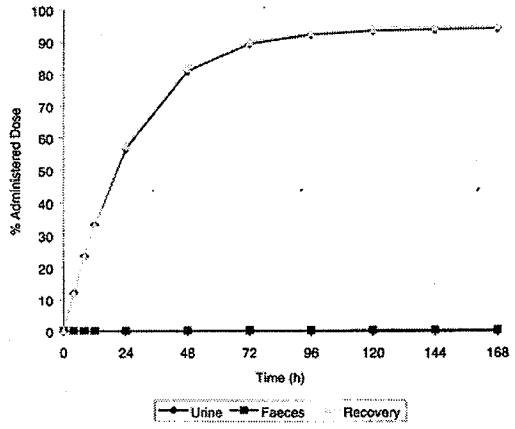
(Table 2 and Figure 3). Excretion of total radioactivity via feces accounted for a mean of 0.4% and 0.3% of the administered dose via oral and IV administration, respectively (Table 2 and Figure 2).

Table 2. Cumulative Recoveryof Radioactivity (Mean ± SD, N=5 at 168 hr post dose).

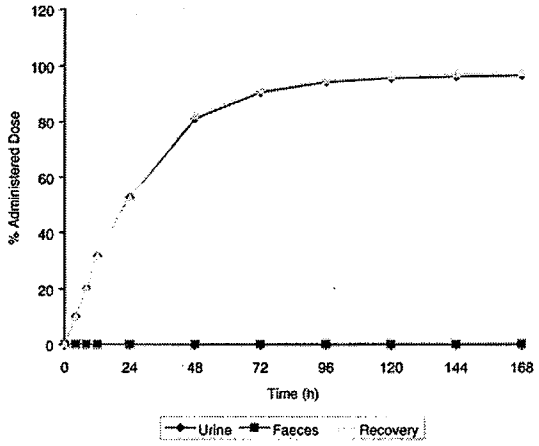
Route	Total Recovery in Urine (% of Dose)	Total Recovery in Feces (% of Dose)	Total Recovery (% of Dose)
IV	96.8 ± 2.6	0.3 ± 0.1*	97.1 ± 2.7
Oral	94.2 ± 3.1	0.4 ± 0.2	94.6 ± 3.1

* Mean included results calculated from data less than 30 dpm above background.

Figure 3. Mean Cumulative Excretion Following Single Oral (a) and Intravenous (b) Administration of [^{14}C]-SPM 927 to Healthy Male Volunteers.



a. Oral



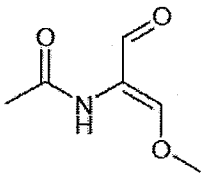
b. IV

Metabolite profiling was conducted with pooled plasma and urine samples. Pooled plasma samples were prepared for each subject by combining a fixed volume of the plasma collected at each timepoint. This gave 0-24 hr samples for each subject. Urine samples were prepared for each subject by combining a fixed percentage of the urine collected at each timepoint. This gave 0-96 hr urine samples for each sample.

Table 3 summarizes the concentrations of parents and metabolites in pooled urine and plasma.

Data indicated that on average, SPM 927 was the main species in plasma with an average of 70-75% of total radioactivity. SPM 12809 was another main species but in much lower quantity with an average of ~3% of total radioactivity. In urine, both SPM 927 and SPM 12809 are major species with 35-45% of total radioactivity, and 30% of total radioactivity, respectively. There was one additional structurally unidentified polar fraction (~20%) excreted in urine. Investigations with [^{14}C]-lacosamide labeled either at the carboxylic or at the benzylic carbon

atom suggest that the polar fraction may be a desbenzylamine derivative (Report 847) (see proposed structure below).



MW 143

Data also indicated that metabolite profiling was comparable between IV and oral suggesting minimal first-pass effect. The data were consistent with the finding that LCM had ~100% oral bioavailability.

In plasma, SPM 927 was the major component following oral administration but desmethyl and desacetyl SPM were also present. SPM 927 was the major component in plasma following IV administration but desmethyl and desacetyl SPM were detected by LC-MS but were not quantifiable.

Table 3: Amounts of the parent compound LCM and its metabolites in plasma and urine following single oral and iv administration.

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

iv=intravenous; n.d.=not determined as no peak of the substance was detected in chromatogram
Note: The sample radioactivity was assumed to be 100%.
Data source: 5.3.1.1.1: SP619 Table 13.11, Table 13.12, Table 13.13, Table 13.14

b(4)

Discussion and Conclusion:

Estimates for the systemic exposure (measured as $AUC_{(0-\infty)}$) were slightly lower following administration of the [^{14}C] oral solution compared with iv administration of the [^{14}C] solution for

b(4)

PK results: Descriptive statistics for PK parameters of LCM are shown in the following table. The median (and range) is shown because of the small sample sizes of N=5 or N=6 per group.

Blood sampling times: Serial blood samples (7 ml) were collected at serial times post dose.

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

Analytical Methodology for Plasma (Validation Report No. — 0584-haav-hp) b(4)
Analytical Site:
Assay Method: LC-MS-MS
Calibration Range: 1-1000 ng/mL
LOQ: 1 ng/mL

Analytical Methodology for Plasma (Validation Report No. — 0584-haav-hu)
Analytical Site: b(4)
Assay Method: LC-MS-MS
Calibration Range: 0.100-20 µg/mL
LOQ: 0.100 µg/mL

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment.

Pharmacokinetic Results: Descriptive statistics for PK parameters of shown Tables 1 and 2.

Table 1: Pharmacokinetic parameters of LCM following single administrations of 100, 200, 400, and 600mg LCM in healthy male subjects

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

LCM=lacosamide
Note: In addition, arithmetic means and standard deviation for $AUC_{(0-tz)}$, C_{max}, and $t_{1/2}$ of LCM are shown in Appendix 2.7.2.5.1.
a One of the 6 subjects randomized to 600mg LCM did not receive trial medication.

Table 2: Summary of PK Parameters

Mean Pharmacokinetic Parameters After Oral Administration of ADD 234037

Dose	100 mg	200 mg	400 mg	600 mg
C_{max} (ng/mL)				
Mean	2255.3	4712.1	8657.0	12498.4
SD	302.1	521.8	702.7	1515.0
Median	2264.6	4548.0	8632.9	11499.7
CV%	13.4	11.1	8.1	12.1
Minimum	1932.5	4348.4	7461.8	11438.3
Maximum	2563.9	5730.4	9370.9	14800.0
N	6	6	6	5
T_{max} (h)				
Mean	2.000	2.833	3.167	3.000
SD	1.095	0.753	0.408	0.000
Median	2.000	3.000	3.000	3.000
CV%	54.772	26.568	12.892	0.000
Minimum	1.000	2.000	3.000	3.000
Maximum	4.000	4.000	4.000	3.000
N	6	6	6	5
AUC_{0-T} (h·ng/mL)				
Mean	44536.7	87014.2	171149.9	252856.4
SD	7980.7	13745.0	22876.4	46797.2
Median	41983.8	85873.6	180456.5	255868.5
CV%	17.9	15.8	13.4	18.5
Minimum	36262.0	68572.0	130272.7	184499.3
Maximum	54253.7	111027.5	192858.4	310440.0
N	6	6	6	5
$AUC_{0-\infty}$ (h·ng/mL)				
Mean	50069.1	95094.9	185765.1	283306.8
SD	11140.9	16744.6	28761.4	61996.0
Median	45428.9	94308.7	195481.3	297699.9
CV%	22.3	17.6	15.5	21.9
Minimum	39347.1	72260.8	136497.7	190491.9
Maximum	65230.5	124279.5	217696.5	356356.1
N	6	6	6	5
λ Values (/h)				
Mean	0.049	0.057	0.057	0.051
SD	0.007	0.012	0.009	0.013
Median	0.052	0.054	0.056	0.046
CV%	14.353	21.344	15.043	25.458
Minimum	0.038	0.048	0.046	0.041
Maximum	0.055	0.080	0.071	0.073
N	6	6	6	5
t_{λ} (h)				
Mean	14.43	12.61	12.37	14.19
SD	2.28	2.15	1.81	2.87
Median	13.31	12.93	12.36	14.99
CV%	15.78	16.87	14.64	20.24
Minimum	12.42	8.62	9.72	9.45
Maximum	18.10	14.40	15.10	16.80
N	6	6	6	5

A comparison of AUC(0-tz) and Cmax between the dose groups presented in the table above shows that the PK parameters increased proportionally with the dose. Other PK parameters (tmax and $t_{1/2}$) of LCM were unchanged at the different doses.

Dose proportionality of AUC(0-tz) and Cmax as well as AUC(0-∞) is also demonstrated by the ratios of mean values between the dose groups.

PK conclusion: The analysis of PK parameters of LCM showed a dose-proportional increase of Cmax and AUC for doses 100 through 600mg. The maximum plasma concentration was reached

between 1 and 4 hours after dosing and the mean terminal half-life was estimated to be approximately 13 hours at all doses.

4.2.2.1.2 Study SP587: Single Dose Tolerance Study with Ascending Oral Doses of SPM927 (Harkoseride) in Healthy Male Caucasian Volunteers

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Study Type: Single dose study.

Clinical Investigator: [redacted] b(4)

Objectives: The primary objective of was to investigate the safety and tolerability of single ascending oral doses of LCM in healthy male subjects. The secondary objective was to determine the PK profile of LCM.

Study Design:
This was a randomized, double-blind (within each dose level), placebo-controlled, sequential-group Phase 1 trial in healthy male subjects with single-dose administration of LCM capsules filled with powder blend. Sixteen subjects were randomized to active treatment with ascending single oral doses of 400mg, 600mg, and 800mg LCM in 3 treatment periods (12 subjects) or matching placebo treatment (4 subjects). For subjects with adverse events at the 600mg dose level, the dose was not increased further in Treatment Period 3 if the investigator considered it inappropriate, and a dose below 600mg could then be administered in Treatment Period 3.

Blood and urine sampling times: Serial blood samples and urine samples were collected for the determination of LCM concentrations in plasma and urine.

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

Analytical Methodology – Plasma (Validation Report No. – ka215)
Analytical Site [redacted] b(4)

Assay Method: LC-MS-MS
Calibration Range: 0.100-20.0 µg/ml
LOQ: 0.100 µg/ml

Analytical Methodology – Urine (Validation Report No. – ka215) b(4)
Assay Method: LC-MS-MS
Calibration Range: 5.00-500 µg/ml
LOQ: 5.00 µg/ml

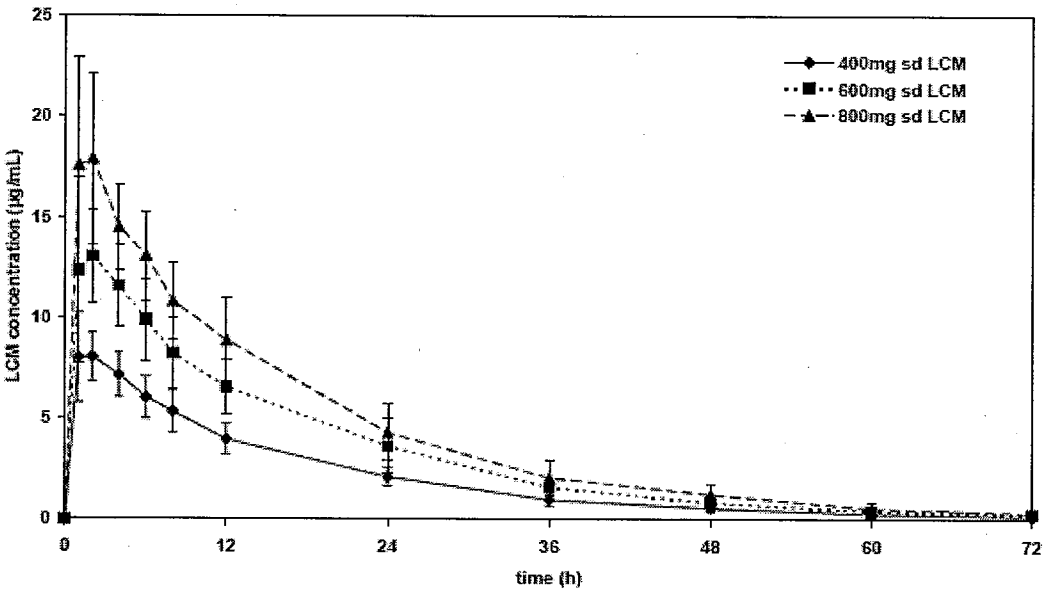
Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOV A) was performed and the 90% confidence intervals were generated for the ratio of fed/fasted 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 doses of 300 mg SPM 927, respectively while 10 and 4 completed the single and multiple dose of 500 mg SPM 927, respectively.

Pharmacokinetics: PK parameters were derived from non-compartmental analysis. Mean PK profiles of SPM 927 for all the treatments are shown in Figure 1. Descriptive statistics for PK parameters of shown Tables 1 and 2.

Figure 1. Mean plasma concentration-time curve of LCM after single oral doses of 400mg, 600mg, and 800mg



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