2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

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NDA number: —
Review number: 1 b(4)
Sequence number/date/type of submission: — , Sept. 28, 2007
Information to Sponsor: Yes ( ) No (X)
Sponsor and/or agent: Schwarz BioSciences, Inc.
Manufacturer for drug substance:

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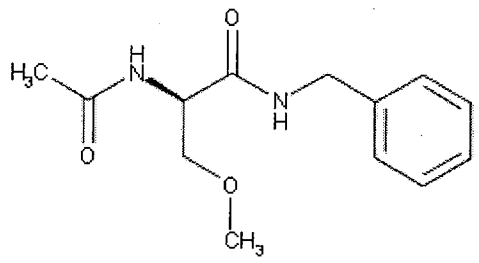
Reviewer name: BeLinda A, Hayes, Ph.D.
Division name: Anesthesia, Analgesia, and Rheumatology Products
HFD #: 170
Review completion date: May 8,, 2008

Drug:

Trade name: Vimpat™
Generic name: Lacosamide
Code name: SPM 927 (Schwarz BioSciences, Inc.), ADD 234937 (NIH/Anticonvulsant Drug Development program), Harkoseride (Harris FRC code)
Chemical name: (R)-2-Acetamide-N-benzyl-3-methoxypropionamide
CAS registry number: 175481-36-4
Molecular formula/molecular weight: $C_{13}H_{18}N_2O_3$/250.30
Structure:



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Relevant INDs/NDAs/DMFs:

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INDs	Status	Division	Indication	Stamp Date	Sponsor
57,939	Active	Neurology Products	Treatment of epilepsy	05/19/1999	Schwarz Biosciences
—	—	Anesthesia, Analgesia and Rheumatology Products	Treatment of neuropathic pain	—	Schwarz Biosciences
68407	Active	Neurology Products	Treatment of epilepsy	10/16/2003	Schwarz Biosciences
73,809	Hold	Neurology Products	Treatment of epilepsy	11/23/2005	Schwarz Biosciences

NDAs	Product	Status	Division	Indication	Stamp Date	Sponsor
22-253	Lacosamide Tablets	Pending	Division of Neurology Products	Adjunctive Therapy Treatment of Partial Onset Seizures in Patients with Epilepsy	09/28/2007	Schwarz Biosciences
22-254	Lacosamide Injection	Pending	Division of Neurology Products	Adjunctive Therapy Treatment of Partial Onset Seizures in Patients with Epilepsy	09/28/2007	Schwarz Biosciences
—	Lacosamide Tablets	—	Division of Anesthesia, Analgesia and Rheumatology Products	Management of Neuropathic Pain Associated with Diabetic Peripheral Neuropathy	—	Schwarz Biosciences

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DMFs №	Subject of DMF	Holder

Drug class: Anticonvulsant

Intended clinical population: Management of neuropathic pain associated with diabetic peripheral neuropathy

Clinical formulation: Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets. They are colored, oval, tablets of different size and are compositionally proportional formulations. The tablets are debossed with "SP" on one side and the tablet strength ("50", "100", "150", "200", "250", "300") on the other side. The composition of the film-coated tablets is described in the table below. b(4)

Component	Function	Tablet Strength (mg)/Color					
		50/Pinkish	100/Dark Yellow	150/Salmon	200/Blue	250/	300
		Amount (mg)					
Lacosamide	Active Ingredient	50.0	100.0	150.0	200.0	250.0	300.0
Cellulose Microcrystalline							
Crospovidone							
Magnesium Stearate							
Hydroxy-propylcellulose							
Total (film-coated tablet)		126.00	252.00	378.00	504.00		

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Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

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Studies reviewed within this submission:

Report №	Study Title	Module/CTD Description
	Pharmacology	
№ N01-NS-4-2311	Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes.	
№ 1001020	Pharmacology Data Report	
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		4.2.1.1/Primary Pharmacodynamics
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№ NO1-NS-4-2311	The profile of anticonvulsant activity and minimal toxicity of ADD 234037 in mice and rat.	
№ A6	Report on in vitro carbonic anhydrase inhibition, change in heart rate and blood pressure in spontaneously hypertensive rats and saluresis/kaluresis in normal rats.	
	Safety Pharmacology	
№ 0200XH15.001	Neuropharmacological profile (NPP) in mice.	**4.2.1.3/Safety Pharmacology**
№ 6958-103	Neuronal vacuolization with SPM 927 in rats.	
№ 020316.TDA	Effect of SPM 927 on cloned hERG Channel expressed in mammalian cells.	
№ 20000377P	SPM927: Evaluation of effect on cardiac action potential in isolated canine purkinje fibers.	
№ A8	The effects of ADD 234037 on the transmembrane potentials of isolated canine ventricular myocytes.	
№ E-014-001	Electrophysiological examination of activity of SPM 927 on the SCN5A-sodium channel expressed in CHO cells.	
№ E-011119.TDA	Effect of SPM 927 on the human cardiac INa (hHNa) current expressed in mammalian cells.	
№ SB01D01	SPM 927: In vitro effect on INa and ICa recorded from human myocytes.	

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№ — 15066/01	Examination of SPM 927 on L-type Ca2+ inward current in isolated ventricular myocytes from guinea pig.	**4.2.1.3/Safety Pharmacology**
№ 0247DH15.001	Cardiovascular (Hemodynamic) evaluation of ADD 234037 in the open-chest anesthetized dog.	
№ 0247DH15.002	Cardiovascular (Hemodynamic) evaluation of ADD 234037 in dogs.	
№ 0247DH15.003	Cardiovascular Evaluation of ADD 234037 in a dog.	
№ 20000376P	Evaluation of haemodynamic effects and electrocardiogram following intravenous dosing in the anaesthetized dog.	
№ 0247XH15.004	Cardiovascular Evaluation of ADD 234037 in non-human primates.	
№ 20000378P	Behavioral Irwin Test and effect on body temperature following single oral administration on the rat.	
№ 20000380P	SPM 927: Evaluation of effect on intestinal transit in the rat following single oral administration.	
№ 20000381 P	SPM 927: Evaluation of interactions with neurotransmitters (Acetylcholine, histamine, serotonin) and barium chloride on isolated ileum of guinea pigs.	
№ 05.237/5	Evaluation of SPM 927 as a discriminative stimulus in a drug discrimination procedure in the rat.	
№ 05.637/4	Evaluation of SPM 927 for abuse potential using an i.v. self-administration paradigm in the rat.	
№ 05.122/6	Evaluation of SPM 927 in the conditioned place preference test in the rat.	
	Pharmacokinetics/Toxicokinetics	
№ 699/46	SPM 927: A study of absorption, distribution, metabolism and excretion following oral administration to the mouse.	**4.2.2.2/Absorption**
№ 18447/04	Single dose pharmacokinetics of SPM 927 in CD®-1 mice.	
№ 18772/05	14-Day toxicokinetics study by oral administration of SPM 927 in CD®-1 mice.	
№ 133418/00	Exposure of the mouse to SPM 927 after single intraperitoneal administration.	
№ 0699/023	[14C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat.	
№ 699/47	SPM 927: A study of absorption, and excretion following oral administration to the rat.	**4.2.2.3/Distribution**
№ F232	Bioavailability and excretion of [14C]ADD 234037 in male beagle dogs following single administration.	
№ 699/48	PM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog.	
№ — 15654/02	Pharmacokinetic study in male beagle dog after repeated (twice daily) oral administration of SPM 927.	
№ 0699/46	SPM 927: A study of absorption, distribution, metabolism and excretion following oral	

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	administration to the mouse.	
№ F212	Absorption, distribution, metabolism, and excretion of [14C]-ADD 234037 in Sprague Dawley rats following either a single intravenous or oral administration.	
№ 0699/48	SPM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog.	
№ 699/23	[14C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat.	
№ 699/15	[14C]-SPM 927: Placental transfer, lacteal secretion and transfer to suckling neonates in the rat.	
№ 699/016	[14C]-SPM 927: In vitro binding to plasma proteins in mouse, rat, dog and human.	
№ 0699/17	[14C]-SPM 927: Quantitative whole-body autoradiography following oral and intravenous administration to the pigmented rat.	
№ 9818851	In vitro metabolism of ADD 234037 using liver microsomes from rat, dog, monkey and human.	**4.2.2.4/Metabolism**
№ 0699/25	[14C]-SPM 927: Metabolism in hepatocytes isolated from mouse, rat, rabbit, dog and man.	
№ 0688	Investigation of the metabolism of SPM 927 in different in vitro models.	
№ 826	SPM 927: Metabolite profiling and identification in the mouse, rat and dog.	
№ BA 555-02	Investigation of the Cytochrome P540 1A2 and 3A4 induction of the compound SPM 927 in cryopreserved human monocytes.	
№ 732	Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes.	
№ M1999-057	An investigation of the potential for harkoseride to inhibit cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.	
№ BA 481-03 and BA 481-03-A1	Interaction of the compounds SPM 927 and SPM 12809 (Dimethyl-SPM 927) with the cytochrome P450 isoforms 1A2, 3A4, 2C9, 2C19 and 2D6.	
№ 865	Inhibition of the cytochrome P450 isoforms 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 and SPM 12809.	
№ 651	Transport of SPM 927 across Caco-2 monolayer – Investigation of P-glycoprotein involvement.	**4.2.2.6/Pharmacokinetic Drug Interactions**
	Toxicology	
No. — 13121/00	Acute Toxicity Study of SPM 927 by Oral Administration to CD-1 Mice.	**4.2.3.1/Single-Dose Toxicity**
No — 17964/04	Acute Toxicity Study of SPM 927 by Single Oral Administration to CD Rats.	
No — 17963/04	Acute Toxicity Study of SPM 927 by Single Intravenous Administration to CD-1 Mice.	
No. 18566-0-800	Acute IV Study of ADD 234037 in Rats.	
№ — 13123/00	13-week Subchronic Toxicity of SPM 927 by Oral Administration to CD-1 Mice.	
№ 148-235	13-week Oral Gavage Subchronic Toxicity Study of	

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	ADD 234037 in Rats.	**4.2.3.2/Repeat-Dose Toxicity**
№ 13227/00	6-Month Chronic Toxicity Study of SPM 927 by Oral Administration to Sprague-Dawley Rats.	
№ 13196/00	12-Month Chronic Toxicity Study of SPM 927 by Oral Administration to Beagle Dogs.	

Studies not reviewed within this submission: The studies below were reviewed by Dr. Ed Fisher for NDAs 22-253, 22-254, — or not deemed pivotal for this indication..

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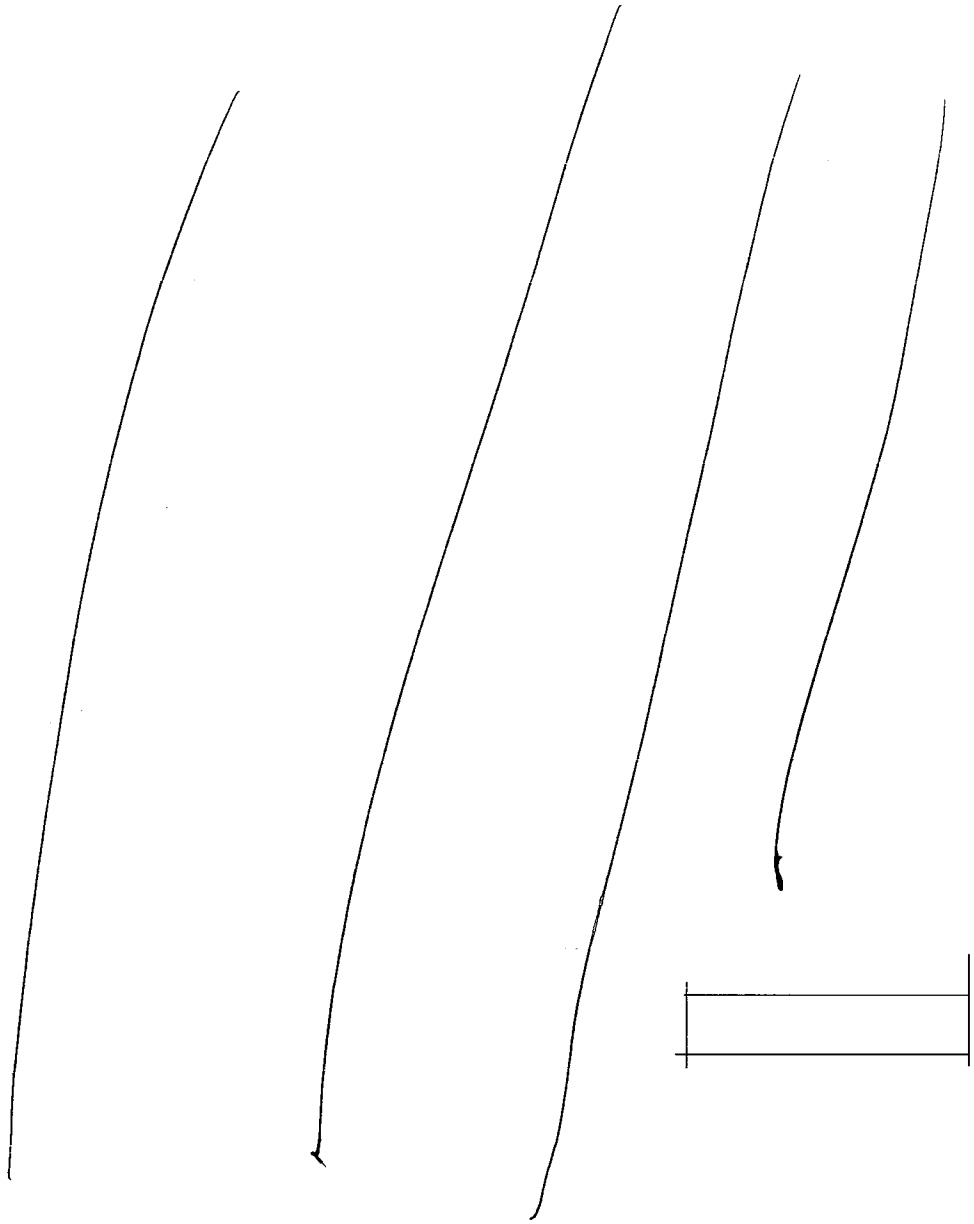

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✓ Trade Secret / Confidential (b4)

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_____ Deliberative Process (b5)

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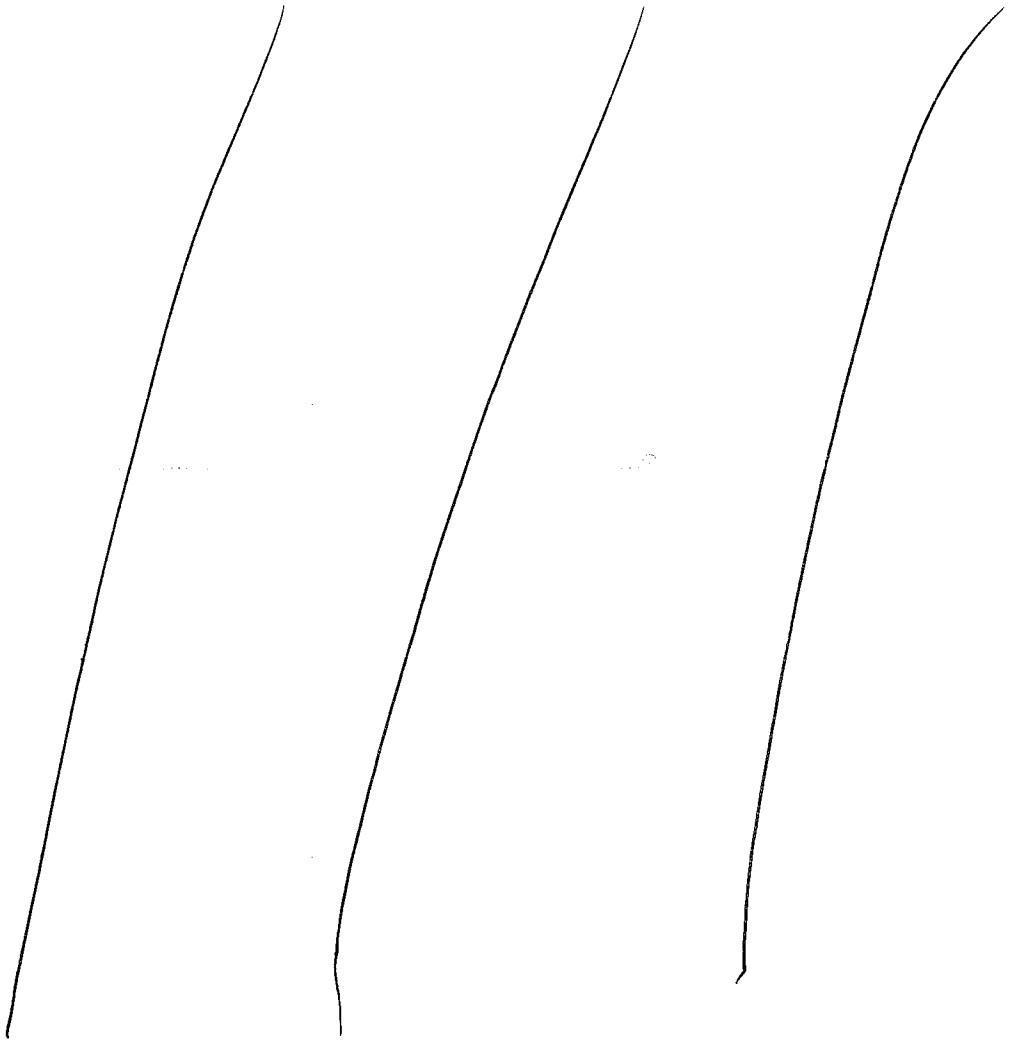

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a member of a series of functional amino acids. The pharmacology of lacosamide has been well characterized using various in vitro and in vivo models. Lacosamide (10-100 μM) did not significantly bind to any of the extensive number of receptors, channels or enzymes tested, including targets that other drugs with anti-epileptic and analgesic activity bind to. Also, lacosamide does not modulate the uptake of neurotransmitters, norepinephrine, serotonin, and dopamine into synaptomes. Lacosamide does not bind to GABA transporters or influence the activity of GABA tranasaminases.

Lacosamide appears to have a dual mode of action. Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation and interacts with collapsin response mediator protein 2 (CRMP-2). Lacosamide-induced enhancement of slow inactivation of voltage-gated sodium channels rediuces the number of sodium channels available and subsequently reduces the excitability of neurons. By enhancing slow inactivation of voltage-gated sodium channels, lacosamide attenuates the excitability of neuron characteristic of both neuropathic pain and epilepsy. Radioligand study with CRMP-2 expressed in Xenopus oocytes showed that lacosamide binds to CRMP-2 with a binding affinity of 5 μM. The diagram below was reproduced from the Sponsor's submission and Beyreutheuther et al. 2007.

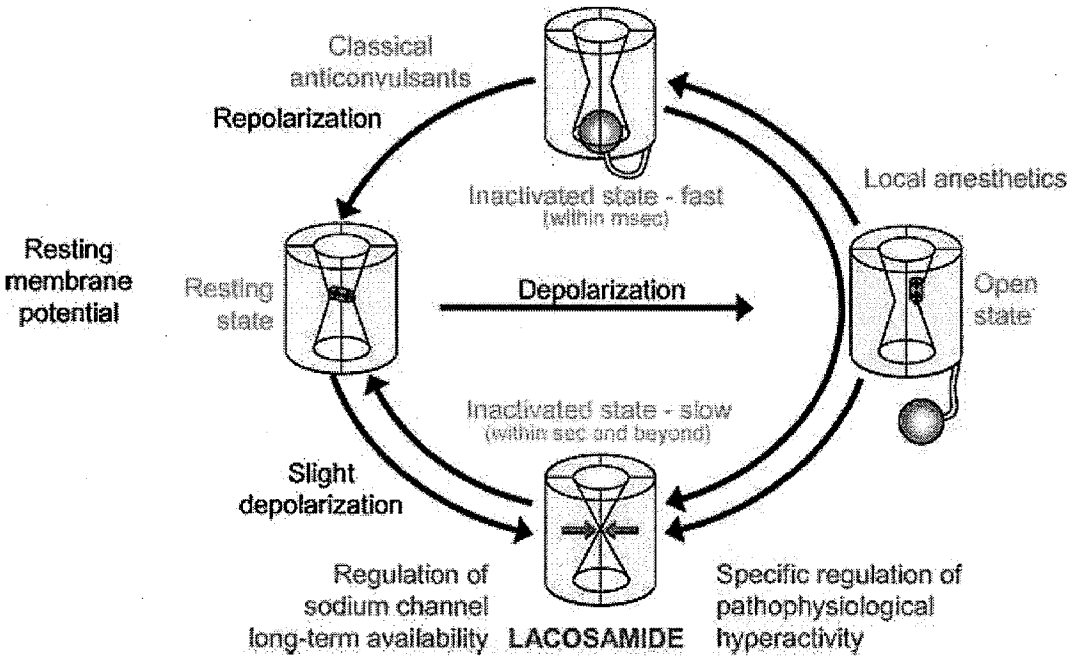

FIG. 2. Physiology of voltage-gated sodium channels. Depending on the membrane potential and the neuronal activity voltage-gated sodium channels are in different states. At the resting potential sodium channels are closed and can be opened by depolarization of the membrane potential allowing the flux of sodium ions into the cell. Within a few milliseconds the channels close from the inside of the neuron and go into the fast inactivated state from which they cannot be activated. When the membrane potential returns to its baseline the sodium channel goes back to its resting state. Under conditions of slight prolonged depolarization and repetitive neuronal activity the sodium channel can go into the slow inactivated state by closing the pore from the inside. This process happens on a second-to-minute time scale. Drugs can either block the open channel (e.g., local anaesthetics), or enhance fast inactivation (classical anticonvulsants) or enhance slow inactivation (lacosamide).

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

To characterize the mechanism of action, the Sponsor conducted radioligand binding, electrophysiological and neurotransmitter release studies. A series of in vitro radioligand studies were conducted to evaluate the binding selectivity of lacosamide (SPM 927), at a concentration of 10 μM, on a wide range of receptors found in the CNS. Results demonstrated that lacosamide did not bind with high affinity (i.e., less than 20% to 10% displacement of binding) to any of the following receptors sites from rodents, bovine, guinea pigs or humans: adenosine, adrenergic (α_1, α_2, β_1, β_2) benzodiazepine, cannabinoid, dopamine, $GABA_A$, $GABA_B$ glutamate, glycine (strychnine-sensitive, strychnine-insensitive), histamine (H_1, H_2, H_3), opioid (δ, κ, μ), muscarinic, (M_1, M_2, M_3, M_4, M_5) and serotonin ($5HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_{1B}$, $5\text{-}HT_3$, $5\text{-}HT_{5A}$, $5\text{-}HT_6$, $5\text{-}HT_7$) receptors. The results from these binding studies are summarized in the table below.

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Lacosamide (SPM 927) binding on various receptors.

Screening Assay of SPM 927 (Lacosamide) Binding					
Study Report/Title	**Neutrotransmitter Receptor**	**Species**	**Tissue**	**Ligand (Concentration)**	**% inhibition of binding at 10 µM**
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Adenosine A_1	Human recombinant	CHO cells	DPCX(1)	< 10%
	Adenosine A_{2A}	Human recombinant	HEK 293 cells	CGS21680 (6)	< 10%
	Adenosine A_3	Human recombinant	HEK 293 cells	AB-MECA (0.1)	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Adenosine	Bovine	Striatum	NECA (4.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Adrenergic$_{\alpha 1}$, non-selective	Rat	Cerebral cortex	Prazosin (0.25)	< 10%
	Adrenergic$_{\alpha 2}$, non-selective	Rat	Cerebral cortex	RX 821002 (0.5)	< 10%
	Adrenergic$_{\beta 1}$	Human recombinant	Sf9 cells	CGP 12177 (0.15)	< 10%
	Adrenergic$_{\beta 2}$	Human recombinant	Sf9 cells	CGP 1277 (0.15)	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Adrenergic$_{\alpha 1}$	Rat	Forebrain	Prazosin (0.50)	≤ 20%
	Adrenergic$_{\alpha 2}$	Rat	Cerebral cortex	RX821002 (1.0)	≤ 20%
	Adrenergic$_{\beta 1}$	Rat	Cerebral cortex	DHA (2.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Benzodiazepine, central	Rat	Cerebral cortex	Flunitrazepam (0.4)	14%
	Benzodiazepine, peripheral	Rat	Heart	PK 11195 (0.2)	<10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Benzodiazepine, central	Bovine	Cerebral cortex	Flunitrazepam (1.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Cannabinoid CB_1	Human recombinant	HEK 293 cells	WIN 55212-2	< 10%
	Cannabinoid CB_2	Human recombinant	HEK 293 cells	WIN 55212-2	<10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Dopamine, D_1	Human recombinant	L cells	SCH 23390 (0.3)	< 10%
	Dopamine , D_1	Rat	Striatum	SCH 23390 (0.3)	< 10%
	Dopamine, D_2	Human recombinant	CHO Cells	Spiperone	< 10%
	Dopamine D_2	Rat	Striatum	Spiperone	< 10%
	Dopamine D_3	Human recombinant	CHO cells	Spiperone	14%
	Dopamine, D_3	Rat recombinant	CHO cells	Spiperone (0.3)	< 10%
	Dopamine, D_4	Human recombinant	CHO cells	Spiperone (0.3)	< 10%
	Dopamine, D_5	Human recombinant	GH4 cells	SCH 23390 (0.3)	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Dopamine , D_1	Rat	Striatum	SCH23390 (0.5)	≤ 20%
	Dopamine, D_2	Rat	Striatum	Sulpiride (3.0)	≤ 20%

Screening Assay of SPM 927 (Lacosamide) Binding (cont.)					
Study Report/Title	**Neurotransmitter Receptor**	**Species**	**Tissue**	**Ligand (Concentration)**	**% inhibition of binding at 10 µM**
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	GABA, non-selective	Rat	Cerebral cortex	GABA (10.0)	< 10%
	$GABA_A$	Rat	Cerebral cortex	Muscimol (5.0)	< 10%
	$GABA_A$, Cl^- channel)	Rat	Cerebral cortex	TBPS (3.0)	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	$GABA_A$	Bovine	Cerebral cortex	GABA (5.0)	≤ 20%
	$GABA_B$	Rat	Cerebral cortex	GABA/isoguavacine (5.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Glutamate (AMPA)	Rat	Cerebral Cortex	AMPA (8.0)	< 10%
	Glutamate (KA)	Rat	Cerebral cortex	Kainic acid (5.0)	< 10%
	Glutamate (NMDA Agonist Site)	Rat	Cerebral cortex	CGP 39653 (5.0)	10%
	Glutamate (PCP)	Rat	Cerebral cortex	TCP (5.0)	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Glutamate (NMDA)	Rat	Forebrain	CGP 39653 (1.0)	≤ 20%
	Glutamate (KA)	Rat	Forebrain	Kainic acid (10.0)	≤ 20%
	Glutamate (AMPA)	Rat	Forebrain	AMPA (5.0)	≤ 20%
	Glutamate (PCP)	Rat	Forebrain	TCP (10.0)	≤ 20%
	Glutamate (MK-801)	Rat	Forebrain	MK-801 (2.60)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Glycine, Strychnine-sensitive	Rat	Spinal Cord	Strychnine (2)	< 10%
	Glycinie, Strychnine-insensitive	Rat	Cerebral cortex	MDL 105,519	< 10%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Glycine, Strychnine-sensitive	Rat	Spinal Cord	Strychnine (16.0)	≤ 20%
	Glycinie, Strychnine-insensitive	Rat	Cerebral cortex	Glycine (10.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Histamine H_1 (central)	Guinea pig	Cerebellum	Pyrilamine (0.5)	< 10%
	Histamine H_2	Guinea pig	Cerebellum	APT (0.10)	< 10%
	Histamine H_3	Rat	Cerebral Cortex	(R)α-Me-histamine (0.5)	< 10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Muscarinic M_1	Human recombinant	CHO cells	Pirenzepine (2)	< 10%
	Muscarinic M_2	Human recombinant	CHO cells	AF-DX 384 (2)	< 10%
	Muscarinic M_3, M_4, M_5	Human recombinant	CHO cells	DAMP (0.2)	< 10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Opiate κ	Human recombinant	HEK 293	U 6953 (0.5)	< 10%
	Opiate µ	Human recombinant	CHO cella	DAMGO (0.50)	< 10%
	Opiate ORL1	Human recombinant	HEK-293	Nociceptin (0.20)	< 10%

№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Purinergic P2X	Rat	urinary bladder	α, β-MeATP (3.0)	< 10%
	Purinergic P2Y	Rat	Brain	dATPαS (0.08)	< 10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Serotonin 5-HT	Rat	Cerebral Cortex	Serotonin (2.0)	< 10%
	Serotonin 5-HT_{1A}	Human recombinant	CHO cells	8-OH-DPAT (0.30)	14%
	Serotonin 5-HT_{1B}	Rat	Cerebral Cortex	CYP (0.10)	< 10%
	Serotonin 5-HT_{2A}	Human recombinant	CHO cells	Ketanserin (2.0)	< 10%
	Serotonin 5-HT_{2C}	Human recombinant	CHO cells	Mesulergine (0.70)	< 10%
	Serotonin 5-HT_3	Human recombinant	HEK-293	BRL 43694 (0.50)	16%
	Serotonin 5-HT_{5A}	Human recombinant	HEK-293	LSD (1.0)	< 10%
	Serotonin 5-HT_6	Human recombinant	HEK-293	LSD (2.0)	< 10%
	Serotonin 5-HT_7	Human recombinant	CHO cells	LSD (4.0)	17%
№ A2/ Thirty-seven receptor binding assays (non-GLP, March 1995)	Serotonin 5-HT_1	Rat	Cerebral Cortex	Serotonin (3.0)	≤ 20%
	Serotonin 5-HT_1	Rat	Cerebrak Cortex	Ketanserin (1.0)	≤ 20%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Sigma σ	Rat	Cerebral Cortex	DTG (8.0)	< 10%
	Sigma σ_1	Guinea pig	Cerebral Cortex	(+)-pentazocine (2.0)	< 10%
	Sigma σ_2	Rat	Cerebral Cortex	DTG (5.0)	< 10%

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The Sponsor submitted several pharmacology studies that used isolated receptors to evaluate the binding affinity of lacosamide and its metabolite SPM 12809 on neurotransmitter transporters. In vitro studies have indicated that lacosamide does not bind to transporters. At a concentration of 10 μM or 100 μM, no significant inhibition (< 30%) of control specific binding occurred on the dopamine, norepinephrine, GABA, and serotonin transporters. The major metabolite SPM 12809 (100 μM), also did not display specific binding to these transporters. Consistent with the radioligand binding studies, in vitro studies using rat synaptosomes revealed that lacosamide (10 μM) did not inhibit neurotransmitter uptake mechanisms for dopamine, norepinephrine, serotonin, or GABA. Nor did lacosamide inhibit GABA transaminase.

Lacosamide binding to transporters

Effects of lacosamide (10 μM) on specific radioligan binding to transporters					
Study Report/Title	**Transporter**	**Species**	**Tissue**	**Ligand (Concentration)**	**% inhibition of binding**
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Dopamine	Human recombinant	CHO cells	GBR12935 (0.50)	< 10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	Norepinephrine	Rat	Cerebral Cortex	Nisoxetine (1.0)	< 10%
	Norepinephrine	Human recombinant	MDCK cells	Nisoxetine (0.3)	< 10%
№ 817003/ Study of SPM 927 in various receptor binding and functional monoamine uptake assays (non-GLP, March 2001)	**Transporter**	**Origin**	**Tissues**	**Ligand (Concentration)**	**% inhibition of binding**
	NE uptake	Rat synaptosomes	Hippocampus	[^{3}H]NE (0.20)	< 10%
	DA uptake	Rat synaptosomes	Corpora Striatum	[^{3}H]DA (0.20)	< 10%
	5-HT uptake	Rat synaptosomes	Brain	[^{3}H]5-HT (0.20)	17%

Lacosamide (SPM 927) and SPM 12809 binding to neurotranmitter transporters

Effects of SPM 927 (100 μM) and SPM 12809 (100 μM) on specific radioligand binding to transporters					
Study Report/Title	**Transporter**	**Species**	**Tissue**	**Ligand (Concentration)**	**% inhibition of binding**
№ 10263/ In vivo pharmacology – Receptor binding assay with SPM 927 and SPM 12809 (non-GLP, August 2005)	Serotonin	Human recombinant	HEK-293 cells	Imipramine (2.0)	SPM 927: -5% SPM 12809: -1%
	Dopamine	Human recombinant	HEK-293 cells	BTCP (4.0)	SPM 927: 28% SPM 12809: 29%
	Norephrine	Human recombinant	HEK-293 cells	Nisoxetine (1.0)	SPM 927: 16% SPM 12809: 16%
№ 6065/ In Vitro pharmacology – Study of SPM 927 (non-GLP, September 2002)	GABA	Rat	Cerebral cortex	GABA (10.0) + isoguvacine (10 μM) + baclofen (10 μM)	-7%

The Sponsor has conducted several pharmacology studies to evaluate the effects of lacosamide on voltage-gated sodium channels and potassium conductance. Briefly, these studies showed that lacosamide modulates sodium channels by selectively enhancing sodium channel slow inactivation without effect on fast inactivation. These data are summarized in the following table.

Study №/Title	Study Assay	Study Outcomes
№ 041012	Radioligand binding assay: CRMP-2 transfected Xenopus oocytes	CRMP-2 transfected Xenopus oocytes possess a binding site for lacosamide with a Kd value of 5 μM.
Errington, 2006	Cultured cortical neurons	Lacosamide produced a significant reduction in the rate of incidence of both sIPSC (Control: 104.7 ± 5.3%, LCM:24.9 ± 9.6%, $P < 0.01$, paired t test, $n = 4$) and sEPSC's (Control: 127.5 ± 16.9%,LCM: 46.1 ± 15.5%, $P < 0.01$, $n = 4$) Concentration-dependent reduction of number of spontaneously arising action potential (IC_{50} = 61 μM)
Errington, 2006	Rat cortical neurons	Lacosamide reduced firing induced by slow (epilepsy-like), bit not fast voltage
Errington, 2006	Mouse N1E-115 neuroblastoma cells	Lacosamide did not show recovery from fast inactivation. Lacosamide in a concentration-dependent fashion enhanced the entry of voltage-gated sodium channels into the slow inactivated state and shifted V_{50} of steady state slow inactivation to more hyperpolarized potentials. Lacosamide did not affect recovery from slow inactivation.
Errington, 2006	Xenopus oocytes expressing rat type II sodium channel (α-subunit).	At 320 μM, lacosamide shifted the V_{50} of steady stated slow inactivation from -43 mV (control) to -58 mV.
F-9938	Chinese hamster ovary cells expressing rat type II sodium channel (α-subunit).	Lacosamide enhanced the maximum probability and shifted the V_{50} of steady state slow inactivation of sodium channels without the effect on fast inactivation.
F-9938	Xenopus oocytes expressing the α-subunit of the human skeletal sodium channel isoform Nav 1.4	Lacosamide had no effect on fast or slow inactivation of NaV 1.4 up to 700 μM.

Drug activity related to proposed indication:

[redacted] b(4)

2.6.2.3 Secondary pharmacodynamics

Nonclinical studies have demonstrated that lacosamide is an effective anticonvulsant in various animal models of epilepsy. Lacosamide demonstrated effectiveness in the genetically susceptible Frings mouse, seizures induced in the maximal electroshock (MES) test in rats and mice or kindled seizures in the rat hippocampal kindling model of partial epilepsy and psychomotor seizures in the mouse 6 Hz model of partial seizures. Effective doses in the MES test (rats 4.5 mg/kg ip, mice 3.9 mg/kg ip) are in a range similar to that reported for other anticonvulsant drugs. Lacosamide at 4.5 mg/kg, i.e., the ED50 for the MES test, significantly elevated the seizure threshold in the intravenous pentylenetetrazole (PTZ) seizure test. It inhibited NMDA-induced seizures and was effective in the homocysteine model of epilepsy. Also, it attenuated kindling development in the amygdala kindling model of epileptogenesis.

2.6.2.4 Safety pharmacology

Neurological effects: The neurological effects of lacosamide (SPM 927, ADD 23407) were characterized in several studies. A summary of these studies is discussed below.

Study Report № 0200XH15.001 (non-GLP compliant). Neuropharmacological profile (NPP) in mice.

The neuropharmacological profile of lacosamide (10 mg/kg, i.p.) was characterized in CD-1 mice (n = 10). The mice were observed for noticeable neuropharmacological signs at 15, 30, and 45 minutes and 1, 2, 3, 4, and 24 hours after dosing. Body temperature was measured 60-minutes post-dosing. Lacosamide did not produce any apparent neuropharmacological signs or effects on body temperature.

Study Report № D00.271/2/A (non-GLP compliant).

The neurobehavioral effects of lacosamide were assessed in rodents in the modified Irwin test. Rats were dosed orally (gavage) with 25, 50 or 75 mg/kg of lacosamide. Battery of neurological parameters examined included: behavioral reactions, motor activity, central excitation, posture, muscle tone, reflexes and autonomic profile. Behavioral parameters were assessed immediately before and at 1, 2, 3, 4, 6 and 24 hours after treatment.

The motor effects of lacosamide were evaluated in mice and rats following oral and intraperitoneal administration in the rotarod test. For intraperitoneal administration male

mice (n = 10/group) and rats (n= 10/group) were treated with a single of 0, 8 16, and 32 mg/kg of lacosamide. The doses tested for oral administration were 0, 32, 64, and 128 mg/kg. Motor coordination was measured by the number of animals falling off a rotating rod and the time to falling off the rod.

Lacosamide impaired motor coordination in mice and rats following both intraperitoneal and oral routes of administration. A dose-dependent impairment in rotarod performance was observed in both species. At the highest dose (32 mg/kg) administered i.p., all mice fell off the rod compared to 1 out of 10 in the vehicle group. The time to falling was reduced from 162.9 ± 17.1 seconds in the vehicle group to 16.9 ± 5.9 seconds in the high dose group. Compared to the vehicle group (5/10), the number of rats falling after the high-dose of lacosamide was 9/10; the time to fall was reduced from 123.9 ± 19.4 seconds to 53.6 ±21.9 seconds.

After oral administration of lacosamide, a dose-dependent decrease in the time to fall off the rotator rod was noted. Significant impairment was observed in mice at a doses of 64 (50.9 seconds vs 136.4 seconds for control) and 128 (28.3 seconds vs 136.4 seconds for control) mg/kg. In rats, a significant effect was observed at a dose of 128 mg/kg (59.4 sec vs 140.8 seconds for control).

The Irwin test was performed in mice and rats to evaluate the effects of lacosamide on behavior, physiological functions and signs of neurotoxicty following oral and intraperitoneal administration. For intraperitoneal administration male mice (n = 3/group) and rats (n= 3/group) were treated with a single dose of 4, 8, 16, 32, and 64 mg/kg and 4, 8, 16, 32, 64 and 128 mg/kg of lacosamide, respectively. Rats were tested with lacosamide orally at doses of 8, 16, 32, 64, 128 and 256 mg/kg. As depicted in the Sponsor's tables reproduced below, lacosamide produced qualitatively similar effects in both mice and rats. These effects included dose-dependent sedation with signs of sensorimotor deficit, abnormal gait, tremors (high dose) and hypothermia. No lethality was observed up to the highest doses tested.

b(4)

Lacosamide effects on the primary observations of the Irwin Test in mice following intraperitonteal administration.

DOSE (mg/kg) i.p.				
4	8	16	32	64
No change	Abnormal gait (rolling) (3/3) at 30'	Sedation + (3/3) 15' → 30' Abnormal gait (rolling) (3/3) 15' → 60' ↓ Muscle tone (3/3) at 30'	Tremor (2/3) → 15' (2/3) at 30' Straub (1/3) at 15' (2/3) at 30' Sedation ++ (3/3) 15' → 30' + (3/3) 60' → 120' Abnormal gait (rolling) (3/3) 60' → 120' Motor incoordination (3/3) → 30' ↓ Reactivity to touch (3/3) 15' → 30' ↓ Muscle tone (1/3) at 30' Akinesia (3/3) 15' → 30' Loss of traction (3/3) 15' → 60' Hypothermia +++ 15' → 30' ++ at 60'	Convulsions (1/3) at 12' (3/3) 15' → 60' Tremor (3/3) < 15' Sedation + (3/3) 120' → 180' Abnormal gait (rolling) (3/3) 120' → 180' ↓ Muscle tone (3/3) at 120' Loss of traction (3/3) 120' → 180' Hypothermia +++ 15' → 60'

(X/N) indicates the number of mice showing the symptoms.
+ = slight; ++ = moderate; +++ = marked.

Observations were performed at 15, 30, 60, 120, 180 minutes and 24 hours after administration.
The symptoms which did not necessitate handling were also observed up to 15 minutes immediately following administration.

Hypothermia was evaluated by comparison of the mean scores obtained in treated and control animals.

b(4)

Lacosamide effects on the primary observations of the Irwin Test in rats following intraperitonteal administration.

DOSE (mg/kg) i.p.					
4	8	16	32	64	128
No change	↓ Muscle tone (3/3) at 15'	Sedation + (2/3) and ++ (1/3) at 30' + (3/3) at 60' Abnormal gait (rolling) (3/3) 15' → 30' ↓ Muscle tone (3/3) 15' → 60'	Sedation + (3/3) at 15' ++ (3/3) at 30' + (3/3) at 60' Abnormal gait (rolling) (3/3) at 30' ↓ Respiration (1/3) at 30' ↓ Muscle tone (3/3) 15' → 180' Hypothermia + at 90'	Tremor (2/3) → 15' (1/3) 30' → 60' (3/3) at 120' Straub (2/3) at 15' Sedation +++ (2/3) 15' → 60' + (1/3) at 15' ++ (1/3) 30' → 60' ++ (3/3) 120' → 180' Abnormal gait (rolling) (1/3) 15' → 30' (2/3) at 180' Motor incoordination (1/3) at 60' (3/3) at 120' Stereotypies (head movements) (1/3) at 120' ↓ Respiration (3/3) → 60' ↓ Fear (2/3) 15' → 60' (3/3) 120' → 180' ↓ Reactivity to touch (2/3) 15' → 30' (3/3) at 60' ↓ Muscle tone (3/3) 15' → 180' Loss of righting reflex (2/3) 15' → 60' Ptosis (2/3) at 120' (3/3) at 180' Exophthalmos (2/3) at 15' (1/3) at 30' Loss of grasping (2/3) 15' → 90' Loss of traction (2/3) 15' → 120' (3/3) at 60' (1/3) at 180' Hypothermia +++ 30' → 60' ++ at 15' and 120' Mydriasis + 15' → 30'	Tremor (3/3) → 15' Sedation +++ (3/3) 15' → 180' ↓ Respiration (3/3) → 180' ↓ Fear (3/3) 15' → 180' ↓ Reactivity to touch (3/3) 15' → 180' ↓ Muscle tone (3/3) 15' → 180' Loss of righting reflex (3/3) 15' → 180' Loss of grasping (3/3) 15' → 180' Loss of traction (3/3) 15' → 180' Hypothermia +++ 15' → 180' Mydriasis + at 180'

(X/N) indicates the number of rats showing the symptoms.
+ = slight; ++ = moderate; +++ = marked.
Observations were performed up to 15 and at 30, 60, 120, 180 minutes and 24 hours after administration.
Hypothermia and mydriasis were evaluated by comparison of the mean scores obtained in treated and control animals.

Lacosamide effects on the primary observations of the Irwin Test in rats following oral administration.

DOSE (mg/kg) p.o.					
8	16	32	64	128	256
No change	Excitation + (2/3) at 30'	↓ Muscle tone (2/3) at 60'	Straub (1/3) 60' → 120'	Straub (1/3) 15' → 30' (2/3) at 60' (1/3) at 120'	Tremor (1/3) at 15' (3/3) 30' → 180'
	Stereotypies (sniffing) (2/3) at 30'		Sedation + (3/3) 30' → 60' + (1/3) at 120'	Sedation + (3/3) at 15' ++ (2/3) and + (1/3) at 30' + (3/3) 60' → 180'	Straub (2/3) at 30' (3/3) at 60'
	Stereotypies (head movements) (1/3) at 30'		Abnormal gait (rolling) (3/3) at 60' (2/3) at 120'	Abnormal gait (rolling) (3/3) 30' → 60'	Sedation + (3/3) at 15' ++ (3/3) at 30' +++ (3/3) 60' → 120' ++ (3/3) at 180'
	↓ Muscle tone (1/3) at 120'		↓ Muscle tone (3/3) 15' → 180'	↓ Reactivity to touch (2/3) at 30'	Abnormal gait (rolling) (3/3) at 15' (1/3) at 30'
				↓ Muscle tone (3/3) 15' → 180'	Loss of balance (2/3) at 30' (3/3) 60' → 180'
				Loss of traction (3/3) at 30'	↓ Respiration (1/3) at 60' (3/3) 120' → 180'
				Mydriasis + at 60'	↓ Fear (3/3) 30' → 180'
					↓ Reactivity to touch (3/3) 30' → 180'
					↓ Muscle tone (3/3) 15' → 24h
					Exophthalmos (1/3) at 15'
					Loss of grasping (3/3) 60' → 180'
					Loss of traction (3/3) 15' → 180'
					Analgesia (1/3) at 30' (2/3) at 60' (1/3) at 120'
					Hypothermia + at 30' +++ 60' → 120' ++ at 180'

(X/N) indicates the number of rats showing the symptoms.
+ = slight; ++ = moderate; +++ = marked.

Observations were performed at 15, 30, 60, 120, 180 minutes and 24 hours after administration.
The symptoms which did not necessitate handling were also observed up to 15 minutes immediately following administration.

Hypothermia and mydriasis were evaluated by comparison of the mean scores obtained in treated and control animals.

Study Report № 6958-103 —— **, GLP compliant).** Neuronal vacuolization with SPM 927 in rats. b(4)

The potential neurotoxic effects of lacosamide were evaluated in — CD®(SD)IGS BR rats (approx. 3 months old). Lacosamide was administered intraperitoneally at doses of 10 and 50 mg/kg. A positive control group was treated with MK-801 (1 or 5 mg). The animals were sacrificed approximately 4 hours or 72 hours after dosing. The posterior cingulated and retrosplenal cortex were histologically examined for signs of neuronal vacuolization and necrosis. b(4)

Brain tissue from lacosamide-treated rats did not show any signs of neuronal vacuolization or cell death at 4 hr or 72 hr, respectively, following single intraperitoneally administration of 10 or 50 mg/kg lacosamide. However, lacosamide-induced clinical signs were observed following the 50 mg/kg dose. These clinical signs included ataxia, dilated pupils, hyperactivity, tremors, and cold to touch. MK-801 treatment resulted in the expected neuronal vacuolization in the retrospinal cortex and posterior cingulated which led to cell death (i.e., necrosis).

Cardiovascular effects: Sixteen in vivo and/or in vitro studies were performed to evaluate the effects of lacosamide on cardiovascular functions in several species. A summary of the primary studies is discussed below. The key findings from these studies are:

- Purkinje fibers: Lacosamide shortening action potential duration that was associated with non-statistically significant decrease in the maximum rate of depolarization (Vmax) suggesting an interaction with the sodium channel.
- Sodium Current (I_{NA}): Lacosamide possesses sodium channel blocking properties. The blocking actions of lacosamide are state-dependent. Lacosamide I_{NA} blocking effects are more pronounced when the sodium channel is in an inactivated state (prevalent at a holding potential of -70 mV (depolarization state)). This effect may be pronounces in subject during myocardial ischemia.
- In vivo studies in anesthetized dogs and monkeys suggest that lacosamide can lower blood pressure, slow intra-atrial conductivity, produce AV-block and AV-dissociation.

Effects on hERG channels.

Study Report № 020316.TDA (GLP compliant). The potential of lacosamide to inhibit potassium current in cardiac action potential duration and QT interval was studied electrophysiologically in vitro using human embryonic kidney cell line (HEK293) that stably expressed human-ether-a-go-go-related (hERG) gene encoded potassium channel on hERG-mediated potassium current were evaluated in voltage-clamped human embryonic kidney (HEK293 cells). Concentrations of lacosamide tested were 10, 100, 300 and 3000 µmol/L.

Relative to the reference drug terfenadine (60 nmol/L), lacosamide was a weak inhibitor of hERG-mediated potassium channel current. Lacosamide did not inhibit hERG current at 10, 100, and 300 µmol/L. At the highest concentration (300 µmol/L) tested, lacosamide elicited a potassium current block of 7% (n=3). Terfenadine, a high-potency blocker, elicited a potassium current block of 76% (n=2). The IC_{50} for the inhibitory effect of lacosamide on hERG current could not be determined because a dose-dependent effect was not observed.

Effects on cardiac action potential parameters.

b(4)

The effects of lacosamide on evoked action potential characteristics and conduction were evaluated in vitro in Purkinje fibers and myocytes isolated from dogs. Results showed that lacosamide induced a dose-dependent decrease in action potential duration in both Purkinje fibers and myocytes.

Study Report № 2000377P (GLP compliant). SPM: Evaluation of effect on cardiac action potential in isolated canine Purkinje fibers.

Isolated Purkinje fibers were perfused with vehicle (15 DMSO in Tryode) and then lacosamide, at increasing concentrations, successively for 25-minute periods at a stimulation rate of 60 pulses per minute (ppm), then for 5 further minutes at a stimulation rate of 12 ppm. The effects of lacosamide on the following cardiac action potential parameters were evaluated at concentrations of $0.15x10^{-5}$, $0.5x10^{-5}$, $1.5x10^{-5}$, $5x10^{-5}$, and $15x10^{-5}$ mol/L: resting potential (RP), amplitude of the action potential, (APA), maximal rate of depolarization (Vmax), and duration of the action potential to 50% (APD50), 70% (APD70) and 90% (APD90) repolarization. The method-control substance cisapride was evaluated at a concentration of $3x10^{-7}$M.

Cisapride ($3x10^{-7}$M) produced effects as expected; increase in action potential duration. Under normal stimulation rate, APD50, APD70 and APD90 were increased by 27 ms, 37 ms and 45 ms, respectively. APD50, APD70 and APD90 were increased by 39 ms, 48 ms and 63 ms, respectively, under low stimulation rate; suggesting a reverse-use dependency. According to the Sponsor, these results are consistent with the testing lab background data.

Lacosamide co-incubation with isolated Purkinje fibers produced no significant treatment-related effect on RP, Vmax and APA under normal (60 ppm) and low (12 ppm) stimulation rates. However, lacosamide induced a dose-dependent decrease in action potential duration. No treatment-related effects on duration of action potential were observed at concentrations of $0.15x10^{-5}$and $0.5x10^{-5}$ mol/L. A statistically significant dose-dependent decrease in APD50, APD70 and APD90 was observed at concentrations of $1.5x10^{-5}$, $5x10^{-5}$, and $15x10^{-5}$ mol/L. As depicted in tables 1 and 2 below, the decrease in action potential was observed under both normal and low stimulation rates. The observed decreases in action potential duration were more pronounced under low stimulation rate than under normal stimulation rate.

The shorten action potential duration was associated with a non-statistically significant decrease in maximal rate of depolarization. The effect on Vmax suggests that lacosamide may have an interaction with sodium channel that is involved in early phase of depolarization.

b(4)

Table 1. Effect of lacosamide on cardiac action potential in isolated canine Purkinje fibers under normal stimulation rate (60 ppm).

Normal Stimulation Rate: 60 ppm							
Treatment		**APA (mV)**	**RP (mV)**	**Vmax (v/s)**	**APD50 (ms)**	**APD70 (ms)**	**APD90 (ms)**
Predose (Tyrode)	Mean	123	-94	491	234	264	295
	SEM	2	1	43	8	10	11
	N	6	6	6	6	6	6
0.1% DMSO in Tyrode	Mean	3	1	-27	-4	-3	2
	SEM	2	1	19	5	4	4
	N	6	6	6	6	6	6
SPM 927 $0.15x10^{-5}$ mol/L	Mean	1	1	-30	-2	-4	-1
	SEM	3	1	19	7	5	4
	N	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS
$0.5x10^{-5}$ mol/L	Mean	-1	2	-79	-7	-8	-5
	SEM	3	1	32	7	5	4
	N	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS
$1.5x10^{-5}$ mol/L	Mean	1	3	-30	-20	-20	-16
	SEM	3	1	22	8	5	4
	N	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	$p \leq 0.05$
$5x10^{-5}$ mol/L	Mean	0	4	-43	-56	-49	-45
	SEM	3	1	25	7	5	4
	N	6	6	6	6	6	6
	P	NS	NS	NS	$P \leq 0.01$	$P \leq 0.01$	$p \leq 0.01$
$15x10^{-5}$ mol/L	Mean	-6	4	-149	-109	-97	-87
	SEM	2	1	56	4	6	5
	N	6	6	6	6	6	6
	P	NS	NS	NS	$P \leq 0.01$	$p \leq 0.01$	$p \leq 0.01$

Table 2. Effect of lacosamide on cardiac action potential in isolated canine Purkinje fibers under low stimulation rate (12 ppm).

Low Stimulation Rate: 12 ppm							
Treatment		**APA (mV)**	**RP (mV)**	**Vmax (v/s)**	**APD50 (ms)**	**APD70 (ms)**	**APD90 (ms)**
Predose (Tyrode)	Mean	119	-89	504	271	311	348
	SEM	3	1	46	18	19	20
	N	6	6	6	6	6	6
0.1% DMSO in Tyrode	Mean	-1	3	-51	-9	-6	-6
	SEM	4	2	26	6	3	2
	N	6	6	6	6	6	6
SPM 927 $0.15x10^{-5}$ mol/L	Mean	-2	3	-105	-0	-2	-2
	SEM	3	2	56	12	7	6
	N	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS
$0.5x10^{-5}$ mol/L	Mean	-2	1	-105	-6	-4	-7
	SEM	3	1	48	12	7	5
	N	6	6	6	6	6	6

b(4)

	P	NS	NS	NS	NS	NS	NS
$1.5x10^{-5}$ mol/L	Mean	-2	5	-65	-17	-18	-23
	SEM	3	1	43	13	9	8
	N	6	6	6	6	6	6
	P	NS	NS	NS	NS	NS	NS
$5x10^{-5}$ mol/L	Mean	-5	7	-104	-83	-71	-70
	SEM	4	2	33	18	9	12
	N	6	6	6	6	6	6
	P	NS	NS	NS	$p \leq 0.01$	$p \leq 0.01$	$p \leq 0.01$
$15x10^{-5}$ mol/L	Mean	-10	5	-165	-142	-126	-109
	SEM	5	2	51	11	12	12
	N	6	6	6	6	6	6
	P	NS	NS	$p \leq 0.01$	$p \leq 0.01$	$p \leq 0.01$	$p \leq 0.01$

Study Report № A8 — 1997, Non-GLP compliant). The effects of ADD 234037 on the transmembrane potentials of isolated canine ventricular myocytes. b(4)

The effects of lacosamide on the following cardiac action potential parameters were evaluated at concentrations of 2.5 and 10 µM: resting potential (RP), time to return to 90% repolarization (APD90), maximal slope phase 0 (Vmax), and overshoot (O).

Lacosamide co-incubation with isolated myocytes produced no significant treatment-related effects on RP overshoot. However, lacosamide induced a consistent decrease in action potential duration. According to the Sponsor, this is an effect consistent with that of dilantin. Lacosamide had no effect on conduction; no treatment-related effect on Vmax was observed.

Effects on cardiac sodium channels.

The effects of lacosamide on sodium channel have been characterized in four in vitro assays: Study Reports E-01-014-001, SB01D01, and 011119.TDA. Results from these studies suggested that lacosamide inhibitory effect on sodium current may be responsible for the observed effects on the action potential in Purkinje fibers. Results from these studies also showed that lacosamide effects on sodium channel were dependent on membrane potential; that is, at more depolarizing potential, lacosamide inhibitory effect was greater. Using recombinant human sodium channels, lacosamide effects demonstrated a frequency dependency.

b(4)

Study Report № E-014-001 (Schwarz BioSciences — 12/19/01-2/01/02). Electrophysiological examination of activity of SPM 927 on the SCN5A-sodium channel expressed in CHO cells.

The mechanism of lacosamide-induced reduction of action potential was elucidated in CHO cells expressing human cardiac sodium channel SCN5A. Electrophysiology activity of the cardiac sodium current was measured using the patch clamp technique in its whole cell mode. The effects of lacosamide on the following current parameters were evaluated at concentrations of 10, 50, 100, 500, and 5000 µM; four replicates were

performed at each concentration except the highest concentration (3 replicates were performed): current amplitude (Imax) and transported charges (Qt). Positive control was lidocaine, a potent inhibitor of SCN5A channels, evaluated at a concentration of 500 μM).

The inhibitory potency of lacosamide was comparable to lidocaine. Lacosamide inhibited sodium current in CHO cells expressing the human SCN5A in a concentration-dependent manner. As depicted in the figures (copied from the Sponsor's submission) below, SCN5A displayed partial inhibition of the sodium current at all concentrations tested. Inhibitory potency (IC_{50}) was dependent on the evaluation method. An IC_{50} of 112 μM and 145 μM and 220 μM and 213 μM was measured for peak current amplitude and transported charge, respectively.

Table. IC_{50} and maximum inhibition for current amplitude and transported charge.

Analysis	IC_{50} (μM)	Max. Inhibition (%)
Imax 1st impulse of 8 series	112 ± 37	53 ± 5
Imax averaged last 5 pulses of 8 series	145 ± 30	67 ± 4
Qt. 1st pulse of 8 series	220 ± 110	53 ± 7
Qt, averaged last 5 pulses of series 8	213 ± 55	66 ± 5

Figure 1. Graphic representation of the analysis of the first transported charge (Qt) of series 8

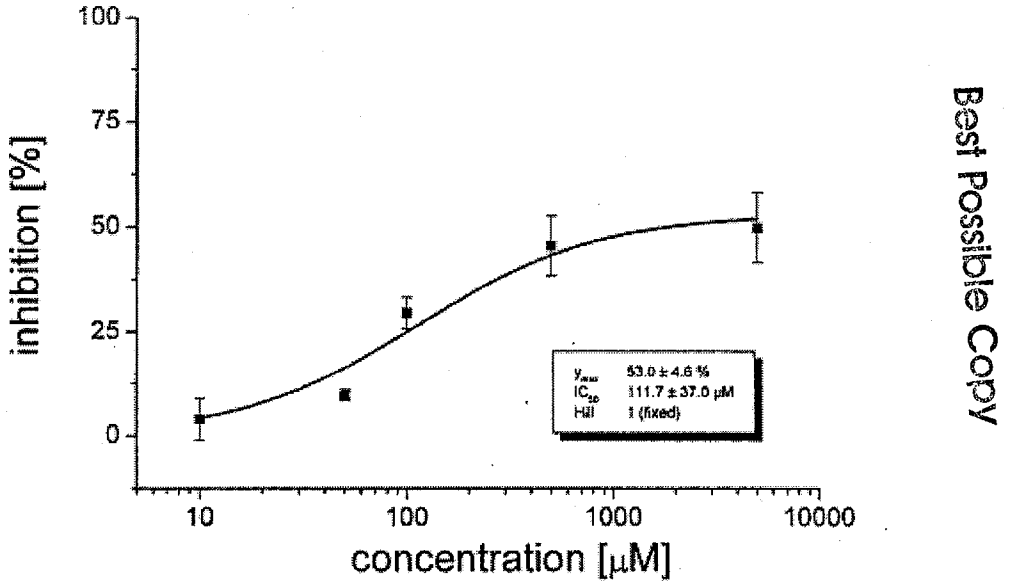


Figure 2. Graphic representation of the analysis of the last 5 pulses averaged current amplitude of series 8

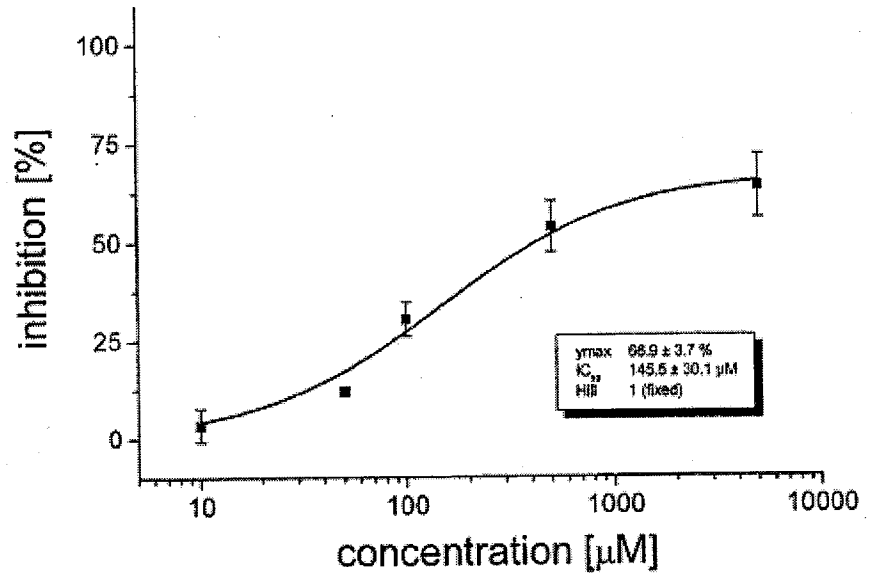
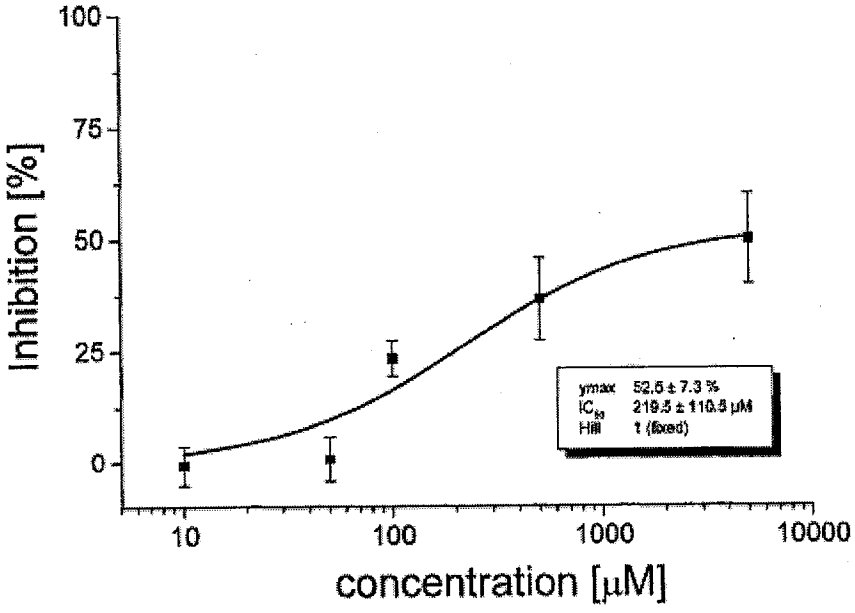


Figure 3. Graphical representation of the analysis of the first pulse transported charge of series 8.



Study Report № E-011119.TDA ——— ., non-GLP compliance, 2002). Effect of SPM 927 on the human cardiac I_{Na} (hHNa) current expressed in mammalian cells. b(4)

The in vitro effect of lacosamide on the hHNa gene that encodes human cardiac Na+ channel was assessed in human embryonic kidney (HEK293) cells expressing the human cardiac sodium channel gene hHNa. Electrophysiology activity of the cardiac sodium current was measured using the voltage clamp technique in cells stably held at –80 mV. The effects of lacosamide were evaluated at concentrations of 10 (n = 2), 100 (n = 3), 200 (n = 7), 500 (n = 5), and 1000 (n = 4) μM. Use-dependence was measured at one concentration of lacosamide (200 μM, n =2). The positive control, lidocaine, was evaluated at a concentration of 2 mM (n = 2).

Lacosamide (10-1000 μM) produced concentration-dependent inhibition in sodium current (Fig 3 copied from the Sponsor). At a concentration of 10 μM, lacosamide produced 9% hHNA blockage. Maximal inhibition leveled off at about 69% at concentrations of 500 and 1000 μM. The IC_{50} for the inhibitory effect of lacosamide on sodium current was estimated to be 293 μM. The positive control, lidocaine produced the expected effects; 100% blockade of I_{Na}.

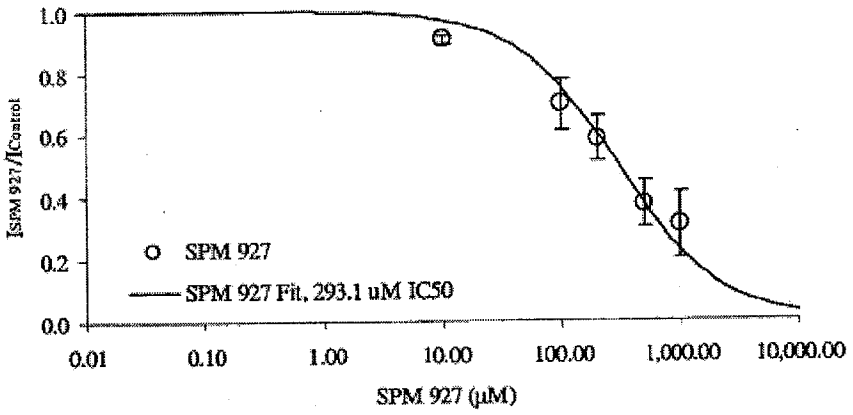


Figure 3. Concentration-response of SPM 927 on hHNa current.
The mean normalized current amplitude ($I_{SPM\ 927}/I_{Control}$) after application of SPM 927 (circles) ± S.E.M versus concentration. Data were fit to a simple 1:1 binding equation (solid line). The estimated IC_{50} was 293.1 μM.

Lacosamide blocked Na channels in a use-dependent manner (Fig 4 copied from the Sponsor). At a concentration of 200 μM lacosamide, repeative stimulation at a frequency of 3 Hz reduced the peak current amplitude by an additional 26%. In contrast lacosamide only produced a block augmentation of 7% in one cell and not the cell at a repeative stimulation frequency of 0.3 Hz.

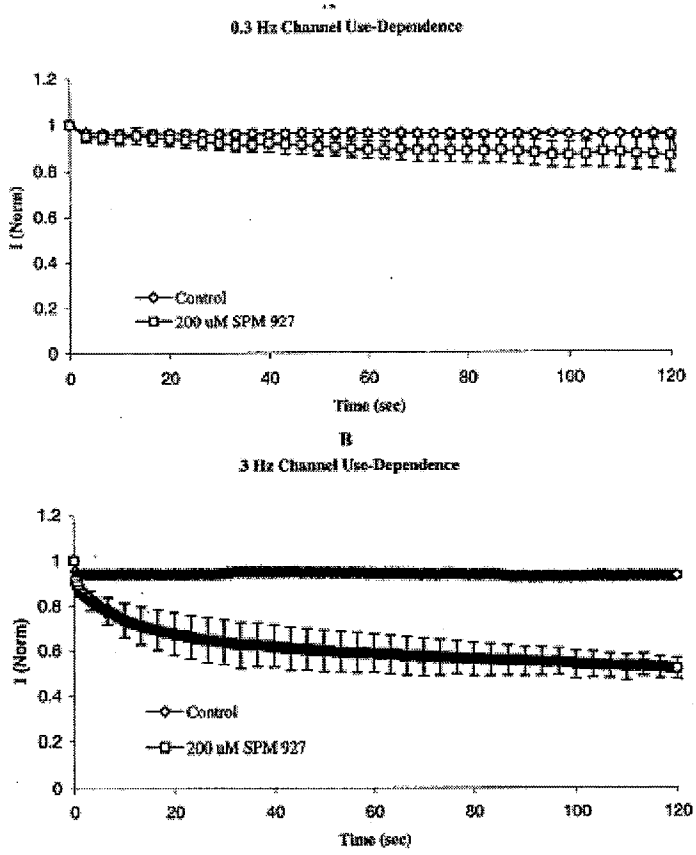


Figure 4. Use-dependence of SPM 927 at 0.3 (A) and 3 Hz (B).
Currents are normalized to the amplitude of the first pulse (mean ± SEM, n=2) in the presence (squares) or absence (diamonds) of 200 µM SPM 927.

Study Report № SB01D01 ~~~ 2002). SPM 927: In vitro effect on I_{Na} and I_{Ca} recorded from human myocytes.

The blocking effects of lacosamide on sodium and calcium currents were evaluated at concentrations of 0.1, 0.3, 1, 3, 10, 100 and 500 µM for I_{Na} and at 10, 100, 5000 µM for I_{Ca} in isolated human atrial myocytes. Electrophysiology activity of the ionic currents was measured using the patch clamp technique in its whole cell mode. Peak inward I_{Na} current was studied in cells using a voltage clamp pulse of 40 ms clamped from the hyperpolarized holding potential of –140 mV or –70 mV. Peak inward I_{Ca} current was studied in cells using a voltage pulse of 200 ms clamped from the holding hyperpolarized potential of –60 mV.

Results suggest that the blocking action of lacosamide on sodium current is state dependent; lacosamide interacts preferentially with inactivated channels. At a holding potential of –140 mV, lacosamide was a weak inhibitor of I_{Na}; less than 10% reduction in

current amplitude was measured at concentrations up to 5 mM; -1.4% ± 2.8% for I_{NA} and -9.9% ± 6.1% for I_{Ca}. In contrast, at a holding potential of –70 mV (large fraction of the channels are in an inactivated state), lacosamide reduced I_{Na} in a concentration-dependent manner; 42% and 100% inhibition occurred at 50 µM and 500 µM, respectively. IC_{50} was 67.5 µM.

Table. Results of lacosamide blocking profile on I_{Na} at 0.1 Hz and a holding potential of –70 mV.

Lacosamide Concentration	% Change[A]	% Reduction ± SE
5 µM	-2.3	0.05 ± 1.4
50 µM	-47.4	-41.7 ± 4.3[B]
500 µM	-90.9	-89.3 ± 2.3[B]
5000 µM	-100	100 ± 0

A: Calculated from the peak current amplitudes after a steady state level of drug block was achieved relative to the current amplitude before drug was introduced (control)
B: Significantly different from control

Effects on cardiac calcium channels.

Study Report № [redacted] 15066/01 ([redacted] b(4)
GLP compliance, 2002). Examination of SPM 927 on L-type Ca^{2+} inward current in isolated ventricular myocytes from guinea pig.

The blocking effect of lacosamide on L-type calcium inward currents was evaluated at concentrations of 15, 50, 150 and 500 µM in isolated guinea pig ventricular myocytes (n = 6 per concentration). Positive control was nifedipine, a potent inhibitor of SCN5A channels, evaluated at a concentration of 1 µM). Electrophysiology activity of the calcium current was measured using the whole-cell patch clamp technique method. Peak inward $I_{Ca(L)}$ current was studied in cells using a pulse of 300 ms duration from the hyperpolarized holding potential of –80 mV.

No lacosamide-related effect on $I_{Ca(L)}$ was observed at concentrations ranging from 15 to 500 µM. In contrast, nifedipine reduced $I_{Ca(L)}$ by approximately 90% within 1 minute after treatment.

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Study Report № A6 ([redacted] non-GLP compliance, 1998). Report on in vitro carbonic anhydrase inhibition, change in heart rate and blood pressure in spontaneously hypertensive rats and saluresis/kaluresis in normal rats.

Spontaneous hypertensive rats (n=2) with systolic blood pressure between 180 and 220 mm Hg were administered a single oral dose of at a dose of 100 mg/kg. Lacosamide effects on blood pressure and heart rate were measure 1, 2 and 4 hours after dosing. There were no treatment-related effects on blood pressure or heart rate.

In Vivo Studies

Study Report № 0247DH15.001 —— non-GLP compliance, 1997). Cardiovascular (Hemodynamic) evaluation of ADD 234037 in the open-chest anesthetized dog. b(4)

One male Beagle dog was anaesthetized with methohexital sodium (10 mg/kg, i.v). Throughout the experiment, anesthesia was maintained through artificial respiration with a mixture of oxygen and isoflurane. Lacosamide at 2.5, 5, 10 and 15 mg/kg was administered consecutively by 1-minute bolus injection. Each dose was administered at least 30 minutes apart. Lacosamide effects on the cardiovascular system were assessed by measuring arterial blood pressure (BP) (systolic (SAP), diastolic (DAP), mean (MAP)), left ventricular end-diastolic pressure (LVEDP), velocity of pressure rise (+dP/dt), cardiac output (CO) and lead II ECG. Hemodynamic parameters were evaluated every minute for the first five minutes and at 5 minute intervals for 25 minutes following each dose of lacosamide. The 10 and 15 mg/kg doses of lacosamide were monitored for an additional 10 and 30 minutes, respectively.

No effects were observed at the 2 mg/kg dose level on any measured parameter. Dose-related decreases in arterial blood pressure (SAP, DAP, MAP), LVP and +dP/dt were observed following administration of 5, 10 and 15 mg/kg lacosamide. MAP was decreased by maximally 10, 15, and 27% following 5, 10 and 15 mg/kg of lacosamide, respectively. LVP was decreased by maximally 10, 11 and 21%, following 5, 10 and 15 mg/kg of lacosamide, respectively. Maximal reductions of +dP/dt amounted to 21, 29 and 38% at concentrations of 5, 10 and 15 mg/kg, respectively. The duration of the effect increased with higher doses. No relevant treatment-related changes were determined for HR, CO and LVEDP. There were n treatment-related effects on ECG parameters at any dose.

Study Report № 0247DH15.002 ——, non-GLP compliance, 1998). Cardiovascular (Hemodynamic) evaluation of ADD 234037 in dogs. b(4)

Beagle dogs (1M and 1F) were anaesthetized with methohexital sodium (10 mg/kg, i.v). Throughout the experiment, anesthesia was maintained through artificial respiration with a mixture of oxygen and isoflurane. Lacosamide at 2.5, 5, 10 and 15 mg/kg was administered consecutively by 1-minute bolus injection. Each dose was administered 30 minutes apart. Lacosamide effects on the cardiovascular system were assessed by measuring arterial blood pressure (BP) (systolic (SAP), diastolic (DAP), mean (MAP)), LVEDP, velocity of pressure rise (+dP/dt), cardiac output (CO) and lead II ECG. Hemodynamic parameters were evaluated every minute for the first ten minutes and at 5 minute intervals for 20 minutes following each dose of lacosamide. The 15 mg/kg dose of lacosamide was monitored for an additional 40 minutes following dosing.

Male. No effects were observed at the 2.5 and 5 mg/kg dose levels on any measured parameter. Dose-related changes in BP, CO and LVP were observed at 10 and 15 mg/kg.

At 10 mg/kg, maximal reduction in MAP (14%), CO (22%) and LVP (14%) were observed. No change in heart rate was observed. No change in HR was observed at 10 mg/kg. At 15 mg/kg, maximal reduction in MAP (51%), CO (64%), LVP (37%) and HR (24%) was observed. The duration of effect varied from 30 to 70 minutes post-dosing. LVEDP was not affected. The marked decreases in MAP, CO and HR appeared at the same time as AV dissociation was observed in the ECG

Female. In the female dog, starting at the lowest dose, lacosamide produced dose-dependent effects on cardiovascular parameters. Lacosamide-related decreases in blood pressure (SAP, DAP, MAP), LVP, and +dP/dt were observed. MAP was decreased maximally by 29 and 59% at 10 and 15 mg/kg, respectively

At 10 and 15 mg/kg, LVP was decreased by 24% and 45% and +dP/dt was decreased by 33% and 78%, respectively. In addition, reductions in HR (-76%, ventricular rhythm) and CO (-81%) were noted following the 15 mg/kg dose. LVEDP was not affected. Duration of effects was dose-dependent. Following the 2.5 and 5 mg/kg dose of lacosamide, the duration of the effect was 30 minutes. Effects observed at 10 and 15 mg/kg sustained through the end of the study. As in the male dog, the pronounced changes in various cardiac performance parameters occurred concomitant with AV dissociation. The female dog died at the conclusion of the 15 mg/kg dose.

Study Report № 0247DH15.003 (—— , non-GLP compliance, 1998). Cardiovascular Evaluation of ADD 234037 in a dog. b(4)

One male Beagle dog was anaesthetized with methohexital sodium (10 mg/kg, i.v). Throughout the experiment, anesthesia was maintained through artificial respiration with a mixture of oxygen and isoflurane. The effect of three consecutive doses of 15 mg/kg lacosamide on hemodynamic parameters was assessed. Lacosamide was administered intravenously over a ten minute infusion period with at least 30-minutes between doses. Lacosamide effects on the following hemodynamic parameters were evaluated: measuring mean arterial blood pressure (MAP) systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), heart rate (HR), lead II ECG and 10 lead ECG.

As depicted in the Sponsor's table reproduced below, treatment-related effects on arterial pressure were observed after each treatment period with lacosamide. Following the first dose of 15 mg/kg of lacosamide, systolic, diastolic and mean arterial pressure was decreased by 23%, 22% and 24%, respectively. There was no treatment-related effect on heart rate. Prior to the administration of the second dose, the parameters were allowed to return to baseline. The effects on blood pressure parameters were similar to those observed after the first dose. Systolic, diastolic and mean arterial pressure was decreased by 22%, 21% and 22%, respectively. Following the third administration of lacosamide, a reduction of 47%, 54% and 53% was observed in systolic, diastolic and mean arterial blood pressure, respectively. The heart rate decreased from 120 beats per minute (bpm) to 57 bpm (-53%, AV dissociation). The marked changes in hemodynamic parameters at the cumulative dose of 45 mg/kg were associated with the appearance of AV dissociation

in the ECG. ECG evaluation revealed a dose-dependent intra-atrial slowing of conductivity. The first dose of lacosamide produced a prolongation of intra-atrial P wave duration from 40 to 80 ms ten minutes post infusion. Similar ECG changes were observed following the second infusion of lacosamide. The same intra-atrial P wave duration was measured after the second dose of lacosamide. During infusion of the third dose (i.e. a cumulative dose of 45 mg/kg), intra-atrial conductivity was further decreased as reflected by an intra-atrial P wave duration of 190 ms at 8 minutes. Two minutes later AV dissociation and a heart rate of 57 bpm were observed. The P wave disappeared 5 minutes after end of the 10-minute infusion. At a cumulative dose of 45 mg/kg, atrioventricular block and dissociation, and abolish surface of lead P waves were noted. Also, it was noted that there was a gradual increase in QRS interval duration and ST segment form changes. These changes may cause QT prolongation.

Cardiovascular evaluation of consecutive doses of 15 mg/kg of lacosamide in a dog.

Treatment	Systolic Arterial Pressure (mm Hg)	Diastolic Arterial Pressure (mm Hg)	Mean Arterial Pressure (mm Hg)	Heart Rate (bpm)
Baseline Values	107	68	83	110
ADD 234037 15 mg/kg, post 10-min infusion	82	53	63	115
30 min post infusion	102	63	77	111
Baseline Values	99	61	75	112
ADD 234037 15 mg/kg, post 10-min infusion	77	48	58	121
30 min post infusion	94	57	71	117
Baseline Values	81	48	60	120
ADD 234037 15 mg/kg, post 10-min infusion	43	22	28	57
40 min post-infusion	77	35	48	66

Study Report № 20000376P [redacted] GLP compliance, 2001). Evaluation of haemodynamic effects and electrocardiogram following intravenous dosing in the anaesthetized dog. b(4)

The objective of this study was to evaluate the potential hemodynamic effects in anaesthetized dogs. Beagle dogs (5M and 5F) were anaesthetized with thiopental plus halothane. Throughout the experiment, anesthesia was maintained with halothane. Lacosamide at 2 (female only), 4, 8, and 12 mg/kg was administered intravenously at regular intervals of 30 minutes over a 30 second period. Lacosamide effects on the cardiovascular system were assessed by measuring arterial pressure (mean, systolic, diastolic), heart rate, cardiac output and derived parameters (stroke volume and total peripheral resistance, left ventricular work), left ventricular pressure (LVP) and derived

parameters (systolic LVP, end-diastolic LVP, dLVP/dt(+) and dLVP/dt(-)), pulmonary arterial pressure, coronary flow and resistance, renal artery flow and resistance, femoral flow and resistance, PR, QT and QTc intervals, QRS complex and arterial pH, pO_2, pCO_2, HCO_3.

Effect of lacosamide on cardiac function in anesthetized dogs

Change in % versus predose value

Parameter	2 mg/kg F only	4 mg/kg M/F	8 mg/kg M/F	12 mg/kg M/F
Mean arterial pressure	-3**	-8**/-7**	-10**/-9**	-13**/-10
Systolic LVP	-4**	-9**/-7**	-11**/-10**	-15**/-9
+dP/dt	-8	-17/-12	-18/-11	-27/-12
-dP/dt	-7	-17/-17**	-15/-25**	-23*/-25
Cardiac output	-5**	-6/-7**	-12**/-11**	-13**/-12
Heart rate (absolute HR predose)	+3* (115)	+6/-+6** (119/117)	+7/+7** (123/119)	+6/+7 (126/120)
PR interval	+3	+4/+6#	+8**/+5#	+16/+6#
QRS duration	+4	+11**/+8*	+17**/+9	+21#/+13#
QT interval	-2**	-4/-3**	-3/-4	-3/-3
QTc (Fridericia)	-1	-3/-1	-2/-2	-1/-1

F = female, M = male; # parameters did not return to baseline prior to dosing

* = p≤ 0.05, ** p≤ 0.001

As depicted in the Sponsor's table reproduced above, treatment-related effects on cardiac function were observed. Lacosamide produced a dose-dependent and short-lasting hypotensive effect at and above 2 mg/kg in females and 4 mg/kg in males. The maximal decreases in MAP at 12 mg/kg were 10% and 13% in female and male dogs, respectively. Lacosamide hypotensive effects appear to be related to its cardiodepressant action as suggested by decreases in systolic LVP, in dLVP/dt(-), left ventricular work, cardiac output, stroke volume and dLVP/dt(+).

In addition to effects on hemodynamics parameters, lacosamide had some effects on ECG parameters. In male dogs, intravenous administration of lacosamide at 4, 8, and 12 mg/kg induced a dose-dependent transient increase in PR interval and QRS complex duration which was statistically significant at 4 and 8 mg/kg lacosamide. The effect at 12 mg/kg was more pronounced, but there were not enough animals to perform statistics. These ECG changes are suggestive of a negative dromotropic action on atrio-ventricular and ventricular conduction. Lacosamide had no effect on QT and QTc intervals (Fridericia correction) at any of the doses tested in male dogs. At 12 mg/kg one male dog out of five showed disturbances of the ECG, manifested as loss of P wave.

In female dogs, lacosamide at 2 mg/kg caused a very slight increase in PR interval duration. At doses of 2 and 4 mg/kg lacosamide induced a slight, but statistically

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significant decrease in QT interval due to a slight tachycardia. QTc interval (Fridericia correction) was not changed. At doses of 4, 8 and 12 mg/kg, lacosamide caused a dose-dependent increase in PR interval and QRS complex duration (statistically significant only at 4 mg/kg due to small animal numbers), indicative of a negative dromotropic action on atrio-ventricular and ventricular conduction, respectively. One first female dog dosed with lacosamide died during the study. She died immediately after receiving the 12 mg/kg dose; death was contributed to a marked drop in arterial blood pressure followed by a cardiac arrest.

Plasma concentrations of lacosamide increased with the dose administered. In male dogs dosed at 4, 8 and 12 mg/kg iv, plasma concentrations of lacosamide ranged from — to — µg/mL, from — to — µg/mL and from — to — µg/mL respectively. In female dogs dosed at 2, 4, 8 and 12 mg/kg iv, plasma concentration of lacosamide ranged from — to — µg/mL, from — to — µg/mL, from — to — µg/mL and from — to — µg/mL, respectively.

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Study Report № 0247XH15.004 (— , non- GLP compliance, 1998). Cardiovascular Evaluation of ADD 234037 in non-human primates.

The objective of this study was to evaluate the potential hemodynamic effects in cynomolgus monkeys. Three male cynomolgus monkeys were anesthetized with ketamine and acepromazine. Throughout the experiment, anesthesia was maintained with pentobarbital (primate № 1) or through artificial respiration with a mixture of oxygen and isoflurane (primate №. 2 and № 3). Primate № 1 was administered lacosamide at 1, 5, 10, and 15 mg/kg. This primate received the high dose three times. The effects of three and four consecutive doses of 30 mg/kg lacosamide were assessed in primate №2 and №3, respectively. Lacosamide was administered intravenously 10 minutes infusion period; 20 minutes elapsed between doses. Lacosamide effects on the cardiovascular system were assessed by measuring arterial pressure (mean, systolic, diastolic), heart rate, lead II ECG and 10 lead ECG.

As depicted in the Sponsor's table reproduced below, lacosamide induced a dose-dependent transient decrease in blood pressure and disturbances of atrial and ventricular conductances.

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Effect of lacosamide on ECG, heart rate and blood pressure and in anesthetized monkeys

Primate number	1x30 mg/kg	2x30 mg/kg	3x30 mg/kg	4x30 mg/kg
1	(1+5+10+15) No effect	(1+5+3x15) No effect	N.D.	N.D.
2	No effect MAP- 14%	QRS amplitude↓ QRS duration ↑ MAP -45%	QRS amplitude↓ QRS duration ↑ MAP -50%	QRS amplitude↓ QRS duration ↑↑ AV block
3	QRS duration ↑ ST deviation loss of Pwave MAP – 14% HR -24%	QRS duration ↑ ST deviation AV block MAP -45% HR -27%	QRS duration ↑ ST deviation ventricular block MAP -50% HR -30%	n.d.

N.D. = not determined; MAP = mean arterial pressure, HR = heart rate

Primate № 1. Lacosamide effects on blood pressure were variable in this primate. Lacosamide had no effects on heart rate and ECG parameters.

Primates № 2 and № 3. In these primates, 30 mg/kg lacosamide induced a transient decrease in mean arterial blood pressure by an average of 16%. Lacosamide produced a reduction in heart rate in primate № 3. No change in heart rate was noted in primate № 2. ECG changes were observed in these primates. After the second dose (cumulative dose of 60 mg/kg) of lacosamide, the mean arterial pressure was dropped by an average of 45%. In primate № 3, heart rate was reduced by 24%. ECG changes were noted in both primates after a cumulative dose of 60 mg/kg. A widening of the QRS complex was observed in both primates. The third primate developed a second degree AV block and displayed a decrease of P wave amplitude, prolongation of QRS complex and deviation ST segment. The third primate did not fully recover to baseline prior to the third dose. Following the third dose of lacosamide, heart rate was decreased by an 18% and 30% in primate № 2 and № 3, respectively. Mean arterial pressure was decreased by an average of 50%. ECG disturbances continued; QRS duration was decreased in both primates. Primate № 3 also developed an intraventricular block.

Pulmonary effects: Study Report № 20000378P ——

b(4)

GLP compliance, 2001). Behavioral Irwin Test and effect on body temperature following single oral administration on the rat.

The effects of oral doses of lacosamide on respiratory parameters using whole body plethysmography were investigated in conscious rats. Single oral doses of lacosamide were administered at 0, (vehicle control), 25, 50 and 75 mg/kg to male rats (n=8/group). To serve as positive control, carbamycholine (30 mg/kg) was administered orally under the same experimental conditions. The respiratory parameters assessed were respiratory rate, peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, tidal volume and airway resistance. Respiration was measured at 5 minute intervals for 10

seconds until 4 hours after drug treatment. Lacosamide had no statistically significant effects on these respiratory parameters compared to the vehicle control group. Carbamycholine treated rats produced the expect changes in respiratory parameters, that is increase in airway resistance, increase in respiratory rate, increase peak inspiratory and expiratory flow and increase tidal volume and a decrease in inspiration and expiration times, demonstrating the validity of the assay.

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Renal effects: Study Report № A6 [redacted], GLP compliance, 1998). Report on in vitro carbonic anhydrase inhibition, change in heart rate and blood pressure in spontaneously hypertensive rats, and saluresis/kaluresis in normal rats.

The effects of oral doses of lacosamide on renal function were evaluated in Long Evans rats. Lacosamide (30 mg/kg) was administered orally to rats (3 per group, male or female) that were hydrated with saline (15 mL/kg, po) prior to dosing. Renal parameters assessed were renal saluresis and kaluresis and urine volume. Hydroflumethiazide (30 mg/kg, po) was used as a positive control. Urine volume was measured over a 6-hour period and analyzed for sodium and potassium ion content. In an in vitro assay, the effect of 10 µmol/L lacosamide on carbonic anhydrase activity from human erythrocytes non- was examined. Lacosamide did not influence urine volume nor induce saluresis or kaluresis within 6 hours after administration compared to vehicle. Hydroflumethiazide treated rats produced the expected changes on renal parameters, that is renal saluresis and kaluresis and urine volume were increased. The activity of carbonic anhydrase was reduced by 21% (n=2), which is considered as no effect in this screening assay.

Gastrointestinal effects: Two studies investigated lacosamide's effects on the gastrointestinal (GI) system.

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Study Report № 20000380P [redacted] GLP compliance, 2001). SPM 927: Evaluation of effect on intestinal transit in the rat following single oral administration.

GI transit time was evaluated in male Wistar rats (n=8/group). Rats were administered single oral doses of lacosamide at 0, 1, 3, 10, 25, 50 and 75 mg/kg 60 minutes prior to the oral administration of a suspension of vegetable charcoal in 2.5% carboxymethylcellulose hydrogel charcoal. Atropine (20 mg/kg) was administered as a positive control. The distance covered by charcoal in the small intestine in the lacosamide treated rats was compared to the vehicle treated rats. Lacosamide elicited a dose-dependent decrease in intestinal motility. A statistically significant effect on the distance covered in the small intestine by charcoal compared to the vehicle control group;7%, 8%, 15%, 28%, 28% and 27% inhibition was observed at 1, 3, 10, 25, 50 and 75 mg/kg respectively. Atropine (20 mg/kg) reduced charcoal transit rate by 47% compared to the vehicle control. This result was consistent with the background data for the reference substance; thus demonstrating the validity of the assay.

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Study Report № 20000381 P (—— GLP compliance, 2001). SPM 927: Evaluation of interactions with neurotransmitters (acetylcholine, histamine, serotonin) and barium chloride on isolated ileum of guinea pigs.

Lacosamide potential interactions with neurotransmitters (acetylcholine, histamine and serotonin) and barium chloride on gastrointestinal contraction were evaluated in vitro in isolated guinea-pig ileum. Lacosamide was tested at $5x10^{-6}$, $1.5x10^{-5}$, $5x10^{-5}$, and $1.5x10^{-4}$M (n=6 assays/concentrations). Method-control substances evaluated under similar experimental conditions were: atropine 10^{-7}M (antagonist method-control substance of acetylcholine-induced contraction), pyrilamine 10^{-7}M (antagonist method-control substance of histamine-induced contraction), cyproheptadine 10^{-5}M (antagonist method-control substance of serotonin-induced contractions) and papaverine 10^{-4}M (antagonist method-control substance of barium chloride-induced contractions).

Under the experimental conditions, lacosamide had no statistically significant effect on contractions induced by acetylcholine ($3x10^{-7}$M), histamine ($3x10^{-7}$M), serotonin ($3x10^{-6}$M) or barium chloride (10^{-3}M) on the isolated ileum of guinea-pigs. Under the same experimental conditions, the method-control substances (atropine 10^{-7}M, pyrilamine 10^{-7}M, cyproheptadine 10^{-5}M and papaverine 10^{-4}M) inhibited, as expected, the contractions induced respectively by acetylcholine, histamine, serotonin and barium chloride, demonstrating the validity of the assay.

Abuse liability: The potential abuse liability of lacosamide was evaluated in drug discrimination paradigm, self-administration paradigm and conditioned placed preference paradigm.

Study Report № 20000380P —— non-GLP compliance 2006). Evaluation of SPM 927 as a discriminative stimulus in a drug discrimination procedure in the rat.

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Nonclinical drug discrimination studies are predictive of drug/substance subjective effects in human and serve as an animal model of intoxication in humans. The objective of this study was to evaluate the abuse potential of lacosamide by assessing its ability to function as a discriminative stimulus and if so, to determine whether known drug of abuse will generalize to the lacosamide stimulus cue.

Drug-naïve Sprague-Dawley rats (n=12) were trained to discriminate between lacosamide (10 mg/kg, i.p., 15-min pre-treatment) and vehicle (physiological saline) under a two-choice operant procedure while responding under a fixed-ratio 10 schedule of food reinforcement. Once the rats attained discrimination criteria (at least 80% of the total responses on the correct (active) lever and fewer than 10(one FR) responses on the inactive lever prior to completion of the FR 10 on the active lever for 5 consecutive or 6 of 7 consecutive training sessions), generalization testing was conducted. Generalization testing was conducted every third day if the rat satisfied criteria 2 days immediately preceding the test day. Selected doses of lacosamide (0.3, 1, 3 and 10 mg/kg, i.p.), diazepam (0.5, 1 and 2 mg/kg, i.p.), morphine (0.5, 1, 2 and 4 mg/kg, i.p.), phenobarbital

(4, 8 and 16 mg/kg, i.p.) and phencyclidine (0.5, 1 and 2 mg/kg, i.p.) were evaluated. For pharmacokinetic analysis, a parallel group of rats (n=3/dose) were administered lacosamide at one of five doses (0.3, 1, 3, 10 and 30 mg/kg, i.p.) or vehicle.

Key Study Findings:

- Lacosamide (10 mg/kg) functioned as a discriminative stimulus effects in rats; rats learned to discriminate between saline and lacosamide. However, it took the animals a long time to meet the discrimination criteria. Discrimination criteria were achieved after a mean average of 59.0 ± 4.2 training sessions.
- Once meeting criteria, the rats continued to show only moderate levels of discrimination between the training dose of lacosamide and saline.
- Results from the generalization tests are reproduced from the Sponsor submission below.

Generalization of SPM 927, diazepam, morphine, phencyclidine and phenobarbital in ra trained to discriminate between SPM 927 (10 mg/kg i.p.) and saline: group summary

Substance (mg/kg i.p.)	% SPM927-lever responding	Rate (responses/sec)
Saline	24.3	0.97 ± 0.12
SPM 927 (0.3)	34.3	1.06 ± 0.13
SPM 927 (1)	31.4	1.09 ± 0.15
SPM 927 (3)	18.4	1.09 ± 0.14
SPM 927 (10)	81.0	0.78 ± 0.10
Diazepam (0.5)	27.8	1.20 ± 0.12
Diazepam (1)	68.8	0.87 ± 0.18
Diazepam (2)	61.3	0.66 ± 0.19
Morphine (0.5)	18.4	1.08 ± 0.12
Morphine (1)	60.1	0.81 ± 0.12
Morphine (1) 2nd test	27.1	0.98 ± 0.13
Morphine (2)	20.8	0.69 ± 0.13
Morphine (2) 2nd test	53.9	0.89 ± 0.13
Morphine (4)	38.2	0.61 ± 0.12
Phencyclidine (0.5)	2.7	1.25 ± 0.15
Phencyclidine (1)	40.1	1.04 ± 0.16
Phencyclidine (2)	0.8	0.55 ± 0.19
Phenobarbital (4)	15.8	1.24 ± 0.13
Phenobarbital (8)	74.1	0.97 ± 0.21
Phenobarbital (16)	*	0.24 ± 0.13

* No mean was calculated as too few (4 of 11) rats responded.

- Generalization testing with doses of lacosamide showed that the lower doses of lacosamide did not generalize to the training dose of lacosamide. Rats

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responded predominately on the saline-appropriate lever; drug-appropriate responding was between 18 and 34%. Only the test dose of lacosamide elicited drug-appropriate responding (81%).

- Diazepam, morphine, phencyclidine and phenobarbital failed to generalize to lacosamide. Following 1.0 mg/kg of diazepam, partial generalization was observed; 68.8% drug-appropriate responding was observed. This partial generalization comprised some animals responding predominately on the drug-appropriate lever with others responding predominately on the saline-appropriate level.
- Morphine at a dose of 1 mg/kg partially generalized to lacosamide stimulus cue; a maximum mean of 60.1% responding on the drug lever occurred. Lower (0.5 mg/kg) and higher (2 and 4 mg/kg) doses of morphine produced comparatively less responding on the drug-appropriate level (between 18.4% and 53.9%). The absence of any clear dose-response relationship, either across all rats or for individual rats suggests that the rats were responding at random.
- Phenobarbital, at a dose of 8 mg/kg, partially generalized to lacosamide. 74.1% lacosamide-appropriate responding occurred. Behavioral disruption was noted at the highest dose (16 mg/kg); rate of responding was markedly decreased (0.24 ± 0.13 resp/sec).
- Based on the results from the generalization tests, the data indicates that the discriminative stimulus produced by lacosamide in rats was not robust or clearly dose-dependent. Thus suggesting that the subjective effects of lacosamide are weak. The generalization testing with drugs with known abuse potential and dependence liability suggest that lacosamide subjective effects are not similar to an opiate, CNS depressant or psychomimetic. Lacosamide subjective effects are not likely to lead to dependence liability and/or abuse.
- Results from the pharmacokinetic studies are presented in the Sponsor's table below.

Mean toxicokinetic parameters of lacosamide and SPM 12809 following a single intraperitoneal administration of lacosamide to the male rats.

Dose	SPM 927			SPM 12809		
[mg/kg]	C_{max} [µg/mL]	t_{max} [h]	AUC_{last} [h µg/mL]	C_{max} [µg/mL]	t_{max} [h]	AUC_{last} [h µg/mL]
0.3	0.34±0.03	0.25[a] (0.25[a])-0.5)	0.51±0.03	<0.100	na	na
1	1.02±0.04	0.25[a] (0.25[a])-0.5)	3.01±1.34	<0.100	na	na
3	3.14±0.30	0.25 (0.25-0.25)[a]	11.4±1.37	0.30±0.05	1 (1-2)	1.69±0.31
10	11.1±1.27	0.25[a] (0.25[a])-0.5)	40.3±3.28	1.26±0.20	2 (2-2)	7.50±0.83
30	40.9±0.87	0.25[a] (0.25[a])-0.5)	138±5.31	3.40±0.16	2 (2-2)	20.0±0.54

a) first sampling time
na denotes not applicable

- Pharmacokinetic analysis showed that all animals were exposed to lacosamide following single dose intraperitoneal administration at 0.3, 1, 3, 10 and 30 mg/kg. Lacosamide was rapidly absorbed. Peak plasma concentrations and

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systemic exposure increased in an approximately dose-proportional manner. At the training dose of 10 mg/kg i.p., Cmax was 11.1 ± 1.27 µg/mL. The major metabolite of lacosamide was also detected, SPM 12809 was observed starting at a dose of 1 mg/kg. The relative exposure to SPM 12809 in plasma represented a fraction of up to 15.1% and 23.1% based on C_{max} and AUC_{last}, respectively.

Study Report № 05.673/4 — non-GLP compliance 2006). Evaluation of SPM 927 for abuse potential using an i.v. self-administration paradigm in the rat.

The ability of lacosamide to function as a positive reinforcer and drug seeking behavior was evaluated in a self-administration paradigm performed in rats. Rats were trained to self-administer cocaine (0.32 mg/kg/infusion) under a fixed ratio 2 schedule of drug reinforcement. After stable responding (defined as a mean of at least 18 infusions over 4 consecutive sessions) was achieved, cocaine was substituted with saline as negative control, then lacosamide, saline and cocaine again. Doses of lacosamide (1, 3 and 10 mg/kg/infusion) were substituted for saline for 10 days or until the number of infusions per session did not vary by more than 20% variation in mean infusions over 4 consecutive sessions or until the number of infusions per session was less than 8 for 4 consecutive sessions.

Key Study Findings:

- Results from the self-administration study are presented in the Sponsor's table below.

SELF-ADMINISTRATION OF COCAINE, SALINE AND SPM 927

Treatment (mg/kg/infusion)	n	Infusions/session (mean ± s.e.m.)
Cocaine (0.32)	27	19.5 ± 0.1
Saline	27	3.4 ± 0.3
SPM 927 (1)	9	3.8 ± 0.9
SPM 927 (3)	9	3.9 ± 0.4
SPM927 (10)	9	1.9 ± 0.3
Saline	27	3.2 ± 0.3
Cocaine (0.32)	27	19.8 ± 0.1

The data show the mean values for the last three sessions of each condition in rats responding under a FR-2 schedule.

- Cocaine maintained self-administration behavior in all rats prior to and after substitution test with lacosamide. The mean number of cocaine infusions was 19.5 ± 0.1 and 19.8 ± 0.1 each daily session before and after tests with lacosamide, respectively.

- Lacosamide failed to function as a positive reinforcer at any of the three doses tested; hence, it did not maintain drug-seeking behavior. When lacosamide was substituted for cocaine, the number of infusions self-administered was similar to that seen during saline sessions. Mean infusions per session was 3.8 ± 0.9, 3.9 ± 0.4 and 1.9 ± 0.3 infusions per session at 1, 3 and 10 mg/kg/infusions of lacosamide, respectively. Mean infusions/session for saline session before and after lacosamide sessions was 3.4 ± 0.3 and 3.2 ± 0.3, respectively).
- Results from this study predict that lacosamide will not elicit reinforcing effects that will produce drug-seeking behavior. Lacosamide did not demonstrate dependence-producing properties.

Study Report № 05.122/6 — GLP compliance 2005). Evaluation of SPM 927 in the conditioned place preference test in the rat. b(4)

The reinforcing properties of lacosamide were evaluated in another behavioral assay, conditioned place preference test, which predict a drug's ability to function as a positive reinforcer. Lacosamide was evaluated at 30 and 100 mg/kg (orally), administered orally 45 minutes before each drug-paired conditioning session. Under similar experimental conditions, morphine (64 mg/kg po, gavage) and vehicle (0.5% hydroxypropyl methylcellulose in distilled water) were tested.

Key Study Findings:

- Lacosamide did not demonstrate reinforcing properties in the conditioned place preference test. Lacosamide did not affect the time spent in the drug-paired compartment during the test session as compared with vehicle control; the animals spent 54% and 58% in the drug-paired chambers following 30 and 100 mg/kg, respectively. The number of crossings was not affected.
- Morphine induced a statistically significant increase (69%) in the time spent in the drug-paired compartment as compared to the vehicle control. The number of crossings was decreased (-42%).
- These results suggest that at the doses of 30 and 100 mg/kg, lacosamide was void of reinforcing properties. In contrast, the reference reinforcing drug, morphine, demonstrated significant positive reinforcing properties.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

The Sponsor did submit study reports for the pharmacological studies conducted. The following table is the reviewer's summary of the pharmacology studies.

7 Page(s) Withheld

1

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The absorption, distribution, metabolism and elimination profiles of lacosamide were investigated in nonclinical toxicity and/or pharmacokinetic studies conducted in mice (CD-1), rats (Sprague-Dawley, Lister Hooded), and dogs (Beagle). The key findings of these studies are listed below:

- Lacosamide is well absorbed following oral administration. Absolute oral bioavailability of lacosamide is high; 94% in male rats and 77% in dogs at a 10 mg/kg dose.

- Urine is the principal route of ^{14}C excretion following [^{14}C]-lacosamide administration. The excretion pattern of [^{14}C]-lacosamide was similar in mice, rats and dogs. In mice, rats and dogs, elimination of [^{14}C]-lacosamide is rapid but prolonged; $\geq$ 40% of the oral dose is present in the 0-24-hr urine sample.

- Routes and rate of excretion of [^{14}C]-lacosamide were similar in males and females following both oral and intravenous administration.

- Lacosamide is excreted in milk. [^{14}C]-Lacosamide-derived radioactivity was excreted in milk following the administration of a single oral dose of 10 mg/kg of [^{14}C]-lacosamide to lactating rats. Concentrations of [^{14}C]-lacosamide-derived radioactivity peaked at 1 hour after oral dosing. Mean milk over plasma ratios ranged between 0.7:1 and 2.5:1.

- Lacosamide is extensively metabolized by the liver as determined in in vivo studies in mice, rats and dogs. The metabolites were found in both the circulation and in excreta in all three species. A total of 17, 25 and 24 metabolites were identified in plasma, urine and feces, respectively, across all species. O-demethylation of lacosamide is the major route of metabolism. The O-demethylated metabolite SPM 12809 was identified as the major metabolite in all species; 32%, 39%, 38% and 2%, 1%, 1% of the excreted dose was observed in mouse, rat, dog urine and feces respectively. In the mouse, the deacetylation metabolite (SPM 6912) and several polar metabolites were identified. In the dog, conjugate metabolites (glucuronirde and sulfates), and hydroxylation metabolites were identified in plasma, urine and/or feces.

- Studies to examine the potential inhibitory effects of lacosamide on human hepatocytes CYP isoforms were conducted with incubation of lacosamide with human hepatocytes at concentrations up to 4000 μmol/L. At a concentration of 100 μmol/L, with the exception of CYP2C19, lacosamide

showed no potential to inhibit the activity of CYP isoforms 1A2, 2A6, 2D6, 2E1, and 3A4 in human hepatocytes at therapeutic concentrations. However, at this concentration, lacosamide significantly inhibited the activity of the CYP2C19 isoforms; 58.9 ± 6.2% inhibition of activity was observed. In another study, lacosamide, in the concentration range of 18 to 4000 μM, displayed inhibitory interactions with CYP isoforms 2C9 (K_i = 6555 μmol/L) 2C19 (K_i = 974 μmol/L) and 3A4 (K_i = 1800 μmol/L).

- Lacosamide itself does not appear to be an inductor of cytochrome P450 enzymes at concentrations of 50 and 500 μmol/L when tested in human hepatocytes. Lacosamide did not induce significant activity of CYP 450 isoforms CYP1A2, CYP2B6, CY2C9, CYP2C19, and CYP3A4.

- Lacosamide is extensively metabolized by the liver as determined in in vivo studies in rats, mice and dogs, and in vitro studies with hepatic microsomes (rat and human) and hepatocytes (mouse, rat, rabbit and human). A total of 17, 25 and 24 metabolites were identified in plasma, urine and feces, respectively, across all species. [^{14}C]-Lacosamide was the predominant component in all profiles with maximum concentrations of 13.7, 12.4 and 8.1 μg eq/mL in mouse, rat and dog plasma, respectively. Major metabolites identified in the plasma of the mouse following a single oral dose of lacosamide were SPM 12809 (M1), SPM 12817 (p-M2), SPM 6912 (M5), a polar peak and an unknown compound. Similar study in rats found these metabolites except M5 and the unknown compound. Major metabolites in the plasma of dogs were M1, p-M2, and a medium polar peak.

- The major pathways of metabolism involved the O-demethylation oxylation of lacosamide to form the major metabolite SPM 12809. Other pathways involve the hydroxylation of lacosamide to form p-M2 and deacetylation of lacosamide to form M5. Possible metabolic pathways of lacosamide are shown in the figure below.

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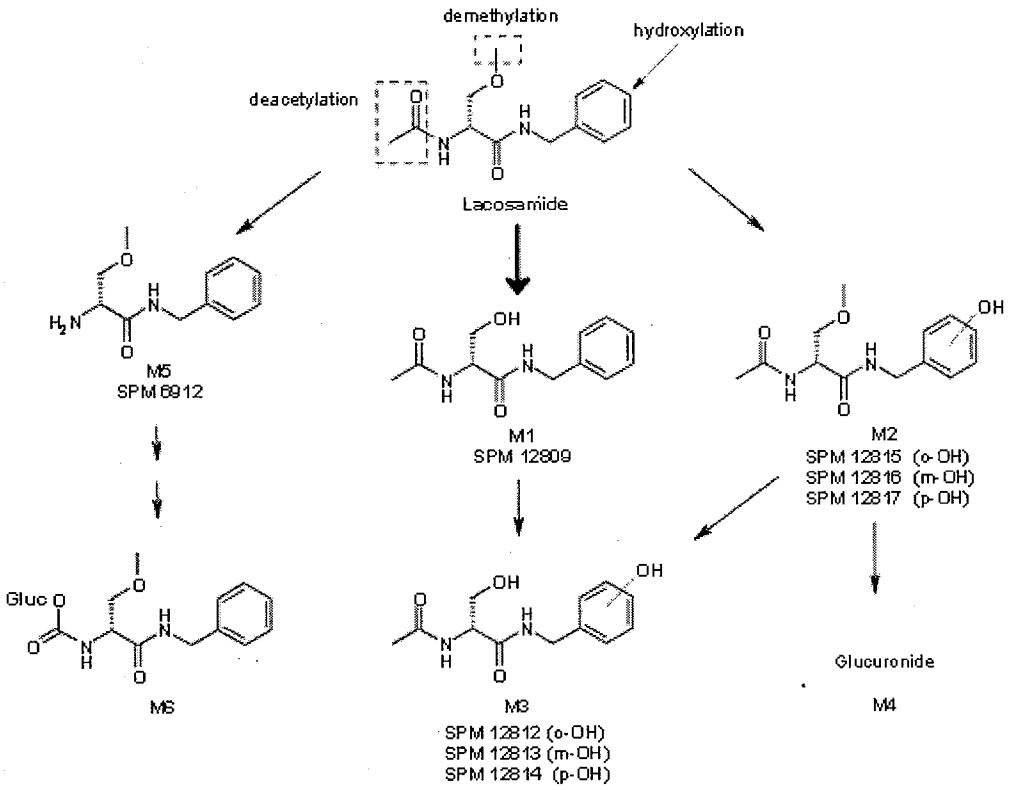
Possible metabolic pathways of lacosamide



- No significant inhibition of major cytochrome CYP450 isoforms is observed up to a lacosamide in vitro concentration of 4000 µmol/L. When recombinant human enzymes were incubated with lacosamide and its major metabolite SPM 12809 at concentrations up to 4000 µmol/L (10 mg/mL) and 10000 µmol/L (2.3 mg/mL), respectively, no or low inhibitory interactions with CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2D6 and CYP2E1 were detectable for lacosamide or SPM 12809. On the other hand, lacosamide and SPM 12809inhibited the following CYP isoforms: CYP2C19 (IC_{50} = 1.8 mmol/L (450 µg/mL)), CYP3A4 (IC_{50} = 2.8 mmol/L (700 µg/mL)), CYP2C9 (IC_{50} =10.2 mmol/ L (2550 µg/mL)), CYP1A1 (IC_{50} = 47.9 mmol/ (11950 µg/mL) and CYP3A5 (IC_{50} = 3.31 mmol/L (830 µg/mL). The potential of lacosamide to inhibit the metabolism of substrates of these CYP isoform is low at therapeutic concentrations because the concentrations of lacosamide required to produce 50% inhibition is greater than 30-fold higher than human lacosamide plasma levels (14.5 µg/mL, Study Report № SP588).

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

Single-dose and repeat-dose absorption studies were conducted in rodents and dogs following oral, intravenous or intraperitoneal administration.

Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral administration to the mouse.

Study №: 699/46

Male and female CD-1 mice (n=30/sex) were administered a single oral dose (20 mg/kg, 5MBq/kg) of [^{14}C]-lacosamide formulated in sterile deionised water at 4 mg/mL. At 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after postdose, three animals of each sex were exsanguinated per time point. Plasma and whole blood were collected for quantification of lacosamide plasma concentration. Radioactivity levels were measured using a —— b(4) —— liquid scintillation counter with a lower limit of qualification of 0.012 µg equivalents/g.

Key study findings:

Sample	C_{max} (µg eq/g)		$T_{1/2}$ (h)		T_{max} (h)		AUC_{0-48h} [h µg eq/g]		AUC_{0-inf} [h µg eq/g]	
	M	F	M	F	M	F	M	F	M	F
Plasma	14.08	18.76	12.90	19.88	1	0.5	75.71	77.56	78.00	83.73
Blood	13.84	17.59	19.50	34.82	1	0.5	77.45	81.00	83.39	97.68

- Following oral administration, absorption of [^{14}C]-lacosamide was rapid. Noticeable levels of [^{14}C]-lacosamide-derived radioactivity was measured at the first sampling time point, 0.25 hours, after oral dosing.
- Plasma concentration of radioactivity reached maximum levels of 14.08 and 18.76 µg eq/g within 1 hour in males and 0.5 hours in females, respectively.
- $T_{1/2}$ (h) in plasma was 12.9 and 19.5 hour in males and females, respectively.
- Blood levels of [^{14}C]-lacosamide-derived radioactivity was approximately similar to that of plasma.

Study Title: Single dose pharmacokinetics of SPM 927 in CD®-1 mice.
Study №: 18447/04

Fasted male CD-1 mice (n=42/group) were administered a single oral dose (20 and 180 mg/kg, 5MBq/kg) of [^{14}C]-lacosamide formulated in sterile 0.5% hyroxypropyl methylcellulose. Terminal blood samples were drawn at 0.5, 1, 2, 4, 6, 8, and 24 hours after postdose, three animals were sacrificed per time point. Plasma samples were analyzed for lacosamide by LC-MS methods with a lower limit of qualification of 95.75

ng/mL (lacosamide), 96.64 ng/mL (Desmethyl metabolite) and 10.39 ng/mL (Desacetyl metabolite).

Key study finding:

Median plasma concentrations and PK parameters following oral administration of a single dose of 20 and 180 mg/kg lacosamide in male mice.

	Median Plasma concentrations (ng/mL) of [^{14}C]-lacosamide-derived radioactivity					
	20 mg/kg			180 mg/kg		
	Lacosamide	Desmethyl metabolite	Desacetyl metabolite	Lacosamide	Desmethyl metabolite	Desacetyl metabolite
Time (h)						
0.5	10328.3	1280.2	444.8	61468.1	4067.5	1584.8
1	9639.3	2097.6	598.4	47675.8	7020.8	2125.8
2	6795.6	2355.7	546.3	37009.7	7531.1	2455.4
4	3801.5	2320.4	336.8	14955.0	7028.7	1672.6
6	1038.5	939.6	101.7	10560.1	5448.2	1011.3
8	290.4	373.9	32.6	7361.5	3094.2	638.0
24	ND	ND	ND	1370.8	1520.8	120.8
t_{max} (h)[a]	0.5	2	1	0.5	2	2
Cmax (ng/mL)	10328.3	2355.7	598.4	61468.1	7531.1	2455.4
AUC_{last} (h*ng/mL)	32557	12641	2400	250256	83564	18146

ND: Not determined a: first sampling time

- Lacosamide was rapidly absorbed after oral administration with radioactivity detected in the plasma in 30 minutes post-dosing.
- T_{max} for lacosamide was achieved within 30 minutes after a single oral administration of 20 and 180 mg/kg.
- Peak plasma concentrations of lacosamide achieved at 30 minutes after administration.
- Peak plasma levels of the desmethyl- and desacetyl- metabolites were reached within 2 hours post-dose after the highest dose.
- The O-demethylation metabolite accounted for 39% and 33% of the systemic exposure (AUC) to lacosamide following the oral administration of 20 and 180 mg/kg, respectively
- The desacetyl metabolite accounted for 7% of the systemic exposure to lacosamide both dose levels.

Study Title: <u>14-Day toxicokinetics study by oral administration of SPM 927 in CD®-1 mice.</u>
Study №: 18772/05

Male and female CD®-1 mice (n=8/sex/group) were orally (gavage) administered lacosamide formulated in sterile 0.5% hyroxypropyl methylcellulose for 14 consecutive days at the following doses 20, 60 and 180 mg/kg. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, and 24 hours postdose, one animal was sacrificed per time point. Plasma concentrations of lacosamide, its desacetyl metabolite and its desmethyl metabolite were measured by LC-MS methods.

Key study findings:

The toxicokinetic parameters of lacosamide (20, 60 and 180 mg/kg) on days 1 and 14 following oral administration for 14 consecutive days

Day	Dose (mg/kg)	C_{max} (µg/mL)		T_{max} (h)		AUC_{last} [h µg/mL]	
		M	F	M	F	M	F
Lacosamide							
1	20	13.518	10.058	1	0.5[a]	33.43[b]	28.30[b]
	60	32.597	16.582	1	0.5[a]	126.9[c]	70.84[b]
	180	46.661	38.914	0.5[a]	2	258.1[c]	224.1[c]
14	20	15.649	12.801	0.5	0.5	35.94	29.16
	60	41.639	29.527	1.0	0.5	122.8	81.43
	180	103.309	32.851	0.5	2	244.3	239.4
Desmethyl metabolite							
1	20	4.193	2.975	2	1	16.12	12.98
	60	9.095	7.239	2	2	39.67	30.61
	180	14.801	10.660	2	4	30.61	82.67
14	20	4.224	2.844	1	2	16.83	9.317
	60	9.871	7.483	2	1	53.90	30.95
	180	20.996	16.221	0.5	2	195.6	195.6
Desacetyl metabolite							
1	20	0.838	0.637	1	2	2.808	2.420
	60	1.697	0.942	2	2	8.332	5.203
	180	3.124	2.563	2	2	18.99	18.99
14	20	0.755	0.654	1	0.5	2.220	1.969
	60	1.248	1.223	1	2	5.873	5.173
	180	2.785	1.660	0.5	2	12.53	19.10

a: First sampling time.
b: Time for calculation was 0-8 hour
c: Time for calculation was 0-24 hour

- Lacosamide was rapidly absorbed with peak plasma concentration being achieved between 0.5 hours and 2 hours post-dosing. Thereafter the plasma levels declined.
- Plasma concentration increased in a dose-dependent manner. A 3-fold increase in dose (20 mg/kg to 60 mg/kg) resulted in an approximate dose-proportional increase in both peak plasma concentrations and systemic exposure in both genders in the intermediate dose group. However, in the high dose, systemic exposure increased in a less than dose proportional 9-fold increase in dose (20 mg/kg to 90 mg/kg) resulted in a less than proportional increase in systemic exposure in both genders; increased between 2.6 and 6.6-fold (Cmax) and between 6.8 to 8.2-fold (AUC_{last}).
- Peak plasma concentrations of both metabolites were observed between 0.5 and 4 hours postdosing. The desmethyl metabolite accounted for 37% to 48% of the levels obtained for lacosamide systemic exposures (based on AUC) in females on day 1. In males, the desmethyl metabolite accounted for 12% to

48% of the lacosamide systemic exposure (based on AUC) on day 1. The desacetyl metabolite represented a small percentage of the lacosamide systemic exposure; 5 to 6% of the systemic exposure (based on AUC) on day 1.

- A gender difference was observed. Exposure in the female mice tended to be slightly lower than in the male mice.

Study Title: Exposure of the mouse to SPM 927 after single intraperitoneal administration.
Study №: 133418/00

Male and female CD®-1 mice (n=10/sex/group) were administered a single intraperitoneal dose (50, 100 and 200 mg/kg) of lacosamide formulated in sterile 0.5% hyroxypropyl methylcellulose. Terminal blood samples were drawn from 2 mice per sex at 5 minutes, 15 minutes, and 1, 2, and 6 hours after dosing. Plasma concentrations of lacosamide were determined by LC-MS/MS methods.

Key study findings:

Dose (mg/kg)	C_{max} (µg/mL)		T_{max} (h)		AUC_{0-6} [h µg/mL]	
	M	F	M	F	M	F
50	63.43	62.72	0.25	0.25	114.8	100.9
100	129.9	119.8	0.25	0.25	255.0	272.4
200	225.9	216.9	0.25	0.25	703.6	767.5[a]

a: n = 1

- Plasma concentration increased in a dose-dependent manner. Peak plasma concentration (C_{max}) increased in approximate proportion to the dose.
- Lacosamide plasma concentrations of the females and males were comparable within each group.
- Lacosamide was rapidly absorbed after intraperitoneal administration with radioactivity detected in the plasma in 15 minutes post-dosing.
- T_{max} was achieved within 15 minutes after each dose of lacosamide.

Study Title: [^{14}C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat.
Study №: 0699/023

The objective of this study was to measure the absorption of [^{14}C]-lacosamide following single and multiple oral administration in Sprague Dawley rats. For the single dosing study, male and female Sprague Dawley rats (n=12/sex) were administered a single oral dose (10 mg/kg, 4.0 MBq/kg) of [^{14}C]-lacosamide formulated in sterile deionised water at 2 mg/mL. At 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours post-

dosing, three animals of each sex were evaluated per time point. For the repeat-dosing study, three male rats per group (n=4) were administered non-radiolabelled lacosamide for six consecutive days followed by a single administration of [$^{-14}$C]-lacosamide. Blood samples were collected at the same time points as for the single oral dosing study. Blood samples were withdrawn from a lateral tail vein and quantification of lacosamide was determined in both plasma and whole blood. Radioactivity levels were measured using liquid scintillation counting.

Key study findings:

	Single Oral Dosing Study									
Sample	**C_{max} (µg eq/mL)**		**$T_{1/2}$ (h)**		**T_{max} (h)**		**$AUC_{0\text{-}168h}$ [h·µg eq/mL]**		**$AUC_{0\text{-}inf}$ [h·µg eq/mL]**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Plasma	7.215	7.847	53.02	72.85	1.5	1.5	79.81	104.2	83.25	116.4
Blood	6.788	7.762	168.4	188.1	1.5	1.5	95.59	112.8	141.7	188.2
	Multiple Oral Dosing Study									
Plasma	7.161	-	61.77	-	2	-	88.47	-	95.51	-
Blood	6.512	-	152.6	-	2	-	100.5	-	149.3	-

- [^{14}C]-Lacosamide is rapidly absorbed following single and multiple oral administrations. T_{max} was 1.5 and 2 hours following single and multiple oral administration, respectively.
- Following a single oral dose of [$^{-14}$C]-Lacosamide, peak plasma levels as well as time to reach maximal plasma concentration in male and female rats were similar. The mean maximum concentration of radioactivity in plasma was 7.215 and 7.847 µg eq/mL in males and females, respectively. The corresponding T_{max} was 1.5 hours for both sexes.
- Levels of radioactivity rapidly declined in both sexes by 12 hours post-dosing. Radioactivity concentrations were approximately 20% of the corresponding maximum; 1.212 and 1.440 µg eq/mL in male and female, respectively. Radioactivity was still detectable at low levels at 168 hour post-dose.
- Systemic exposure was slightly higher in female animals. AUC values for the female blood and plasma were all approximately 1.2 to 1.4 times the value for males. Mean plasma $AUC_{(0\text{-}\infty)}$ h µg eq/mL was 83.25 and 116.4 for males and females, respectively. Mean blood $AUC_{(0\text{-}\infty)}$ h µg eq/mL was 141.7 and 188.2 in male and female, respectively.
- Lacosamide had a long terminal half life ($T_{1/2}$); 168.4 (males) and 188.1 (females) hours.
- The AUC and $T_{1/2}$ values for the multiple dose administration study were comparable to the values obtained for the males in the single oral dosing study.

Study Title: SPM 927: A study of absorption, and excretion following oral administration to the rat
Study №: 699/47

Male and female Sprague Dawley rats (n=3/sex) were administered a single oral dose (40 mg/kg, 5 MBq/mg) of [^{14}C]-lacosamide formulated in sterile water. At 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dosing, three animals of each sex were analyzed per time point. Blood were withdrawn from a lateral tail vein and quantification of lacosamide was determined in both plasma and whole blood. Radioactivity levels were measured using liquid scintillation counting. The limit of quantification was 0.074 µg equivalents/kg.

Key study findings:

Pharmacokinetic parameters of radioactivity following a single oral administration of (^{14}C)-lacosamide to male and female rats at a nominal dose level of 40 mg/kg.

Sample	Cmax (µg eq/g)		$T_{1/2}$ (h)		T_{max} (h) (range)		$AUC_{0\text{-}48h}$ [h·µg eq/g]		$AUC_{0\text{-}inf}$ [h·µg eq/g]	
	M	F	M	F	M	F	M	F	M	F
Plasma	17.72 ± 1.675	17.11 ± 2.774	21.64 ± 4.140[a]	46.95 ± 41.73a	6 (4-6)	4 (0.5-12)	266.4 ± 17.84	328.0 ± 53.96	296.4 ± 24.34[a]	448.7 ± 123.8[a]
Blood	16.19 ± 0.390	16.19 ± 1.230	56.40 ± 17.30[a]	43.79 ± 21.31[a]	4 (2-4)	4 (4-12)	268.8 ± 21.07	299.1 ± 35.17	396.6 ± 22.30[a]	441.0 ± 34.79[a]

a: The data were such that calculations of the parameters $T_{1/2}$ and $AUC_{0\text{-}inf}$ is based on two concentrations only, so no great reliance should be placed on these data.

Blood and plasma concentrations of radioactivity following a single oral administration of (^{14}C)-lacosamide to male and female rats at a nominal dose level of 40 mg/kg.

	µg equivalents of [^{14}C]-lacosamide			
	Plasma		Blood	
	Males	Females	Males	Females
Time (h)				
0	BLOQ	BLOQ	BLOQ	BLOQ
0.25	8.163 ± 3.512	9.585 ± 4.270	7.344 ± 3.260	8.363 ± 3.531
0.5	10.42 ± 3.726	11.78 ± 4.206	9.478 ± 3.451	10.85 ± 3.928
1	12.81 ± 3.630	13.59 ± ±2.127	11.96 ± 3.459	12.84 ± 2.121
2	13.50 ± 2.829	13.00 ± 1.576	12.97 ± 2.808	12.80 ± 1.711
4	16.98 ± 0.743	15.47 ± 0.595	16.18 ± 0.389	15.57 ± 0.357
6	16.77 ± 3.172	14.93 ± 2.012	15.07 ± 1.500	14.39 ± 1.972
8	14.31 ± 2.355	14.50 ± 1.552	13.90 ± 2.155	13.57 ± 3.907
12	10.77 ± 2.452	14.68 ± 4.972	10.50 ± 2.520	13.37 ± 3.907
24	2.141 ± 0.606	2.559 ± 0.448	2.260 ± 0.612	2.517 ± 0.509
48	0.963 ± 0.194	1.752 ± 0.110	1.617 ± 0.249	2.525 ± 0.862

- Absorption of orally administered [^{14}C]-lacosamide was rapid; relatively high concentrations of radioactivity were measured in the plasma at the first sampling time (0.25 hours) after dosing.
- At 4 to 6 hours after dosing, there was evidence of secondary elevation of both plasma and blood levels of radioactivity thus suggesting the possibility of entero-hepatic recirculation of radiolabelled moieties or, possibly, two routes absorption.

- Following a single oral administration of [^{14}C]-lacosamide dose level of 40 mg/kg, plasma levels of radioactivity reached mean maximum concentrations of 17.7 and 17.1 µg equivalents/g within 5.5 hours of dose administration for males and females respectively.
- Blood levels of radioactivity mimicked those in plasma and reached mean maximum concentrations of 16.2 µg equivalents/g within 7 hours of dose administration for males and females respectively

Study Title: Bioavailability and excretion of [^{14}C]ADD 234037 in male beagle dogs following single administration.
Study №: F232

Three male Beagle dogs received 10 mg/kg (0.54 MBq/kg) [^{14}C]-lacosamide orally and intravenously. Initially the dogs were administered [^{14}C]-lacosamide orally and after an 8-day washout period, the dogs were administered an intravenous dose of [^{14}C]-lacosamide. At predose, 0.167, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, and 48 hours post-dosing, blood was collected from the jugular vein. Quantification of total radioactivity in both plasma and whole blood was determined by LCS. The tables below (reproduced from the Sponsor's submission.) shows the plasma and blood concentration of [^{14}C]-lacosamide-derived radioactivity following oral and intravenous administration.

Table 2. Concentration of [^{14}C]ADD 234037-derived radioactivity in blood and plasma of male Beagle dogs following oral administration. Results expressed as mean ± SD of concentration (µg equiv/g).

Time Point (h)	Animal No. 201M	202M	203M	Mean ± SD
Blood				
Predose	0.000	0.000	0.000	0.000 ± 0.000
0.167				3.424 ± 3.921
0.5				6.014 ± 4.506
1				8.575 ± 3.951
1.5				11.745 ± 3.352
2				11.414 ± 2.104
3				10.270 ± 0.228
5				7.112 ± 0.154
8				3.809 ± 0.229
12				1.810 ± 0.141
24				0.534 ± 0.037
48				0.096 ± 0.167
Plasma				
Predose	0.000	0.000	0.000	0.000 ± 0.000
0.167				4.275 ± 4.210
0.5				7.430 ± 4.469
1				10.515 ± 3.607
1.5				14.023 ± 3.621
2				13.760 ± 2.370
3				12.471 ± 0.876
5				8.501 ± 0.377
8				4.591 ± 0.199
12				2.129 ± 0.051
24				0.681 ± 0.040
48				0.352 ± 0.032

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Table 4. Concentration of [^{14}C]ADD 234037-derived radioactivity in blood and plasma of male Beagle dogs following intravenous administration. Results expressed as mean ± SD of concentration (µg equiv/g).

Time Point (h)	Animal No. 201M	202M	203M	Mean ± SD
Blood				
Predose	0.000	0.000	0.000	0.000 ± 0.000
0.167				15.709 ± 0.615
0.5				14.751 ± 0.261
1				13.591 ± 0.383
1.5				12.509 ± 0.827
2				11.658 ± 0.960
3				9.738 ± 1.373
5				6.799 ± 1.522
8				4.078 ± 1.232
12				2.054 ± 0.820
24				0.623 ± 0.105
48				0.393 ± 0.090
Plasma				
Predose	0.000	0.000	0.000	0.000 ± 0.000
0.167				17.721 ± 1.431
0.5				16.601 ± 1.116
1				15.638 ± 0.778
1.5				14.576 ± 0.809
2				13.420 ± 0.880
3				11.635 ± 1.090
5				7.942 ± 1.334
8				4.706 ± 1.289
12				2.305 ± 0.878
24				0.717 ± 0.070
48				0.423 ± 0.096

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Key Study Findings:

- [^{14}C]-lacosamide is readily absorbed following both oral and intravenous administration. The rate of absorption [^{14}C]-lacosamide-derived radioactivity was variable. This variability is most likely due to the nonfasted state of the dogs.
- Following oral administration, maximum concentration of [^{14}C]-lacosamide-derived radioactivity were observed in the blood (10.024 to 14.394 µg equivalents/g) and plasma (12.438 to 17.397 µg equivalents/g) between 1-3 hours after dosing.
- Maximum concentration of [^{14}C]-lacosamide-derived radioactivity were observed in the blood (15.042 to 16.253 µg equivalents/g) and plasma (16.169 to 18.987 µg equivalents/g) at 0.167 hour following intravenous administration.
- [^{14}C]-lacosamide-derived radioactivity was readily absorbed following oral administration with a bioavailability between 82 and 97%.

Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog
Study №: 699/48

The absorption of 10 mg/kg (5.0 MBq/kg) [^{14}C]-lacosamide was evaluated in male and female beagle dogs following orally and intravenously administration. Initially the dogs (n=2/sex) were administered [^{14}C]-lacosamide orally and after a 4-week-day washout period, the dogs were administered the intravenous dose of [^{14}C]-lacosamide. Following oral administration, blood was collected from the jugular vein at predose, 10 and 30 minutes, 1, 2, 4, 8, 12, 24, and 48 hours post-dosing. Blood was collected from the jugular vein at predose, 5, 15 and 30 minutes, 1, 2, 4, 8, 12, 24, and 48 hours after intravenous administration. Quantification of total radioactivity in both plasma and whole blood was determined by LCS. The limit of quantification for plasma and blood was 0.013 µg equivalents/g and 0.016 µg equivalents/g, respectively.

Key Study Findings:

- Results from this study were consistent with the results observed in Study № F232, [^{14}C]-lacosamide was readily absorbed following oral administration. [^{14}C]-lacosamide-derived radioactivity was detectable at the first sampling time (10 minutes) following oral administration; mean maximum plasma concentration was achieved within 1 hour. Blood concentrations of [^{14}C]-lacosamide-derived radioactivity was similar to those in the plasma; thus suggesting that radioactivity was not associated with the cellular fraction of blood. This variability is most likely due to the nonfasted state of the dogs.
- The bioavailability of the oral dose was 78.86% and 77.22% in males and females, respectively.

Plasma and blood concentrations and pharmacokinetic parameters following oral administration of [^{14}C]-lacosamide to male and female dogs at a nominal dose level of 10 mg/kg.

	Mean concentrations			
	µg equivalents of [^{14}C]-lacosamide			
	Plasma		Blood	
	Males	Females	Males	Females
Time (h)				
0	BLOQ	BLOQ	BLOQ	BLOQ
0.17	3.239	8.477	4.319	3.795
0.5	8.739	9.613	7.621	6.395
1	11.01	8.757	7.712	7.066
2	9.450	7.553	7.064	5.881
4	5.445	4.226	4.077	3.309
8	1.633	1.221	1.400	1.094
12	0.627	0.394	0.550	0.371
24	0.146	0.102	0.135	0.093
48	0.054	0.044	0.059	0.042
t_{max} (h)	1.0	0.75	0.75	0.75
Cmax (µg equiv/g)	11.01	9.679	7.7226	7.0939
$t_{1/2}$	16.77	19.28	20.06	21.15
AUC(0-t) (µg equiv.h /g)	55.30	44.94	44.13	35.63
AUC(0-∞) (µg equiv.h/g)	56.61	46.17	45.84	36.91
F (%)	78.86	77.22	-	-

Plasma and blood concentrations and pharmacokinetic parameters following a single intravenous administration of [^{14}C]-lacosamide to male and female dogs at a nominal dose level of 10 mg/kg.

	Mean concentrations			
	µg equivalents of [^{14}C]-lacosamide			
	Plasma		Blood	
	Males	Females	Males	Females
Time (h)				
0	BLOQ	0.013	BLOQ	BLOQ
0.08	17.81	16.23	13.66	12.29
0.25	16.40	15.07	12.47	10.47
0.5	16.48	14.71	10.69	10.33
1	15.25	13.90	11.08	10.63
2	12.98	11.88	9.253	8.467
4	7.666	7.312	5.768	5.321
8	2.710	2.434	1.965	2.027
12	1.123	0.981	0.958	0.842
24	0.231	0.202	0.189	0.200
48	0.074	0.068	0.073	0.065
t_{max} (h)	0.08	0.08	0.08	0.08
Cmax (µg equiv/g)	17.81	16.23	13.66	12.29
$t_{1/2}$	14.65	16.03	18.17	15.02
$AUC_{(0-t)}$ (µg equiv.h /g)	86.99	79.16	64.88	61.14
$AUC_{(0-\infty)}$ (µg equiv.h/g)	88.55	80.69	66.80	62.53

- Following oral administration, maximum concentration of [^{14}C]-lacosamide-derived radioactivity of 11.0 (males) and 9.7 (females) µg equivalents/g were achieved within 1 hour after oral administration. Maximum blood concentration of 7.7 (males) and 7.1 (females) µg equivalents/g was within 0.75 hours
- Maximum concentration of [^{14}C]-lacosamide-derived radioactivity were observed in the blood (13.66 (males) and 12.29 (females) µg equivalents/g) and plasma (17.8 (males) and 16.23 (females) µg equivalents/g) at 0.08 .hour following intravenous administration.
- [^{14}C]-lacosamide-derived radioactivity was readily absorbed following oral administration with a bioavailability of > 77%.

Study Title: Pharmacokinetic study in male beagle dog after repeated (twice daily) oral administration of SPM 927
Study №: —— 15654/02 b(4)

The objective of this study was to characterize the pharmacokinetics of lacosamide after two daily oral dosing. The absorption of 12 and 16 mg/kg lacosamide was evaluated in male beagle dogs (n=5) following orally (gelatin capsule) administration. Initially the dogs were administered lacosamide orally at a dose of 12 mg/kg (phase 1) twice daily every 12 hours for eight consecutive days (only one dose was administered on day 8) followed by a washout period of 14 days. Each dog received a total of 15 doses. After the washout period, the dose of lacosamide was increased to 16 mg/kg (phase 2; dose selected based on observed clinical signs in phase 1). The dosing regimen was identical to phase 1 dosing schedule. For each phase, plasma samples were collected every 12

hours after the first administration of lacosamide on day 1 and 8. Blood was collected from the vena cephalics at the following sampling times during phases 1 and 2: on treatment day 1 at predose, 0.5, 1, 2, 4, 8, and 12 (immediately prior to the 2nd dosing) hours post-dosing; on treatment day 8 at predose (prior to the 15th dosing), 0.5, 1, 2, 4, 8 and 12 hours post dosing. Urine was collected prior to the inititiation of treatment and on the 4th treatment day during each phase for approximately 11.5 hours after morning dosing. Quantification of lacosamide and desmethylacosamide (SPM 12809) in both plasma and whole blood was determined by HPLC-Electrospray MS. The limit of quantification for both lacosamide and SPM 12809 in plasma was lower than 40 ng/mL.

Key Study Findings:

- Lacosamide pharmacokinetic parameters and plasma concentration for phases 1 and 2 are presented below (copied from Sponsor's submission).
- Lacosamide was rapidly absorbed following oral administration.
- No accumulation of lacosamide was observed after repeated oral administration of lacosamide twice daily every 12 hours for eight consecutive days.

Tab. 2 Descriptive statistics of SPM 927 plasma concentrations and pharmacokinetic parameters following twice daily oral administration of SPM 927 at 12 mg/kg/treatment (phase 1)

Day	Admin.	Time [hour]	Descriptive Statistics med	min	max	mean	SD	CV
1	1	0	0	0	0	0	0	NA
		0.5	13942.0			13425.1	1362.4	10%
		1	11603.5			12362.9	2235.3	18%
		2	9633.9			9476.2	1413.1	15%
		4	2933.3			3168.1	830.2	26%
		8	465.7			485.7	227.5	47%
		12	121.3			125.6	41.7	33%
8	15	0	0			0	0	NA
		0.5	9478.0			8521.0	5381.0	63%
		1	11845.8			9835.2	5384.4	55%
		2	8677.7			10385.4	3120.3	30%
		4	3186.3			4389.4	2799.2	64%
		8	419.2			702.1	731.0	104%
		12	84.3			140.5	175.0	125%

Day	Admin.	Parameter	Unit	Descriptive Statistics med	min	max	mean	SD	CV
1	1	C_{max}	[µg/mL]	14.21	11.18	15.28	13.85	1.57	11%
		t_{max}	[h]	0.50	0.50	1.00	0.60	0.22	37%
		AUD(0-12h)	[h*µg/mL]	40.71	34.70	50.03	42.05	6.06	14%
		C_{trough} (C_{12h})	[µg/mL]	0.12	0.08	0.19	0.13	0.04	33%
		$t_{1/2}$	[h]	1.77	1.54	1.88	1.72	0.14	8%
		AUC(0-inf)	[h*µg/mL]	41.13	34.91	50.41	42.33	6.12	14%
		CL	[L/h/kg]	0.29	0.24	0.34	0.29	0.04	14%
		Vz	[L/kg]	0.69	0.61	0.88	0.71	0.12	17%
8	15	C_{max}	[µg/mL]	13.01	11.85	15.69	13.55	1.62	12%
		t_{max}	[h]	1.00	0.50	2.00	1.10	0.55	50%
		AUD(0-12h)	[h*µg/mL]	40.41	34.34	60.58	43.47	10.07	23%
		C_{trough} (C_{12h})	[µg/mL]	0.08	0.00	0.44	0.14	0.17	125%
		$t_{1/2}$	[h]	1.53	1.05	1.82	1.48	0.29	20%
		AUC(0-inf)	[h*µg/mL]	40.43	34.43	61.72	43.82	10.52	24%
		CL	[L/h/kg]	0.30	0.19	0.35	0.28	0.06	20%
		Vz	[L/kg]	0.66	0.45	0.68	0.60	0.11	18%
8:1	15:1	R		0.99	0.93	1.21	1.03	0.11	11%

NA not applicable

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Tab. 4 Descriptive statistics of SPM 927 plasma concentrations and pharmacokinetic parameters following twice daily oral administration of SPM 927 at 16 mg/kg/treatment (phase 2)

Day	Admin.	Time [hour]	Descriptive Statistics med	min	max	mean	SD	CV
1	1	0	0	0	0	0	0	NA
		0.5	5476.8			7612.3	6121.0	80%
		1	18380.7			17609.4	3441.9	20%
		2	15318.4			14626.3	1808.3	12%
		4	7818.2			7434.2	1523.3	20%
		8	1873.0			1862.6	653.2	35%
		12	457.6			552.8	307.7	56%
8	15	0	0			11.98	26.79	224%
		0.5	10817.7			10449.2	5209.4	50%
		1	16274.8			16700.0	1827.2	11%
		2	13526.7			13654.9	1829.5	13%
		4	5925.9			6564.2	1965.8	30%
		8	657.7			881.2	590.8	67%
		12	110.5			156.0	114.9	74%

Day	Admin.	Parameter	Unit	Descriptive Statistics med	min	max	mean	SD	CV
1	1	C_{max}	[µg/mL]	18.38	15.32	21.06	18.11	2.67	15%
		t_{max}	[h]	1.00	1.00	2.00	1.20	0.45	37%
		AUD(0-12h)	[h*µg/mL]	73.72	56.94	76.44	69.81	7.96	11%
		C_{trough} (C_{12h})	[µg/mL]	0.46	0.29	1.08	0.55	0.31	56%
		$t_{1/2}$	[h]	1.96	1.89	2.80	2.11	0.39	18%
		AUC(0-inf)	[h*µg/mL]	75.31	57.59	78.64	71.56	8.71	12%
		CL	[L/h/kg]	0.21	0.20	0.28	0.23	0.03	14%
		Vz	[L/kg]	0.67	0.56	0.82	0.68	0.11	16%
8	15	C_{max}	[µg/mL]	16.27	15.19	19.80	16.70	1.83	11%
		t_{max}	[h]	1.00	1.00	1.00	1.00	0.00	0%
		AUD(0-12h)	[h*µg/mL]	58.07	51.42	86.71	61.76	14.26	23%
		C_{trough} (C_{12h})	[µg/mL]	0.11	0.08	0.36	0.16	0.11	74%
		$t_{1/2}$	[h]	1.43	1.28	1.67	1.44	0.15	10%
		AUC(0-inf)	[h*µg/mL]	58.27	51.61	87.58	62.10	14.55	23%
		CL	[L/h/kg]	0.27	0.18	0.31	0.27	0.05	19%
		Vz	[L/kg]	0.54	0.44	0.64	0.55	0.09	16%
8:1	15:1	R		0.80	0.78	1.13	0.88	0.15	17%

NA not applicable

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2.6.4.4 Distribution

Tissue distribution of SPM 927 was evaluated in rodents and dogs following oral or intravenous administration.

Study Title: [^{14}C]-SPM 927: In vitro binding to plasma proteins in mouse, rat, dog and human.
Study №: 699/016

The extent of [^{14}C]-lacosamide binding to plasma proteins and extent of plasma/blood cell partitioning was evaluated in vitro in mouse, rat, and dog. The partitioning of [^{14}C]-lacosamide to red blood cells of mouse, rat, dog and human blood was determined at concentrations of 1.5, 4.5, 9, 15, 30 and 60 µg/mL. The equilibrium time of [^{14}C]-lacosamide binding to mouse, rat, dog and human red blood cells was determined in fresh whole blood incubated with concentrations of 1.5 or 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. In vitro binding of [^{14}C]-lacosamide to plasma proteins was determined at drug concentrations of 1.5, 4.5, 9, 15, 30 and 60 µg/mL using the equilibrium dialysis technique. Duplicate

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portions were subjected to equilibrium dialysis against phosphate buffered saline (pH 7.4) for *ca* 4 hours.

Key Study Findings:

- The overall mean plasma protein binding was very low and non-saturable in the mouse, rat and human; percent of drug bound to plasma proteins was 6.2%, 5.1%, and 6.1% in mouse, rat, and human plasma, respectively.
- Binding to dog plasma protein was low with an overall mean plasma protein binding of 16.5%. Some degree of saturation was observed; ranging from 20.2% at the lowest concentration (1.5 µg/mL) to 11.1% at the highest concentration (60 µg/mL).
- The mean blood cell partitioning of [^{14}C]-lacosamide was 49%, 44%, 47% and 54% in mouse, rat, dog and human respectively.
- Lacosamide was roughly equally distributed in whole blood and plasma in mouse, rat and human. The overall mean blood to plasma ratio was 1.011, 0.991, 0.870, and 0.978 in mouse, rat, dog and human, respectively.

Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral administration to the mouse.
Study №: 0699/46

The distribution of [^{14}C]-lacosamide following a single oral dose of 20 mg/kg (5 MBeq/kg) was characterized in male and female CD-1 mice (n=6/sex). One mouse of each gender was euthanatized by cold shock followed by deep anesthesia under isofluorane at 0.5, 1, 4, 8, 24 and 72 hours. While under anesthesia, blood was obtained by cardiac puncture to obtain plasma to measure the level of radioactivity in plasma. All mice were prepared for quantitative whole-body autoradiography to assess tissue distribution. The lower limit of quantification was between 0.059 µg equivalents/g (males) and 0.069 (females) with an accuracy of ± 15%. The table below shows the distribution of lacosamide in males and females.

Key Study Findings:

- Concentrations of radioactivity in select tissues are presented in the table below. Distribution was extensive; all tissues were exposed to radioactivity at first time point (i.e., 0.5 hours) after dosing.
- The highest concentrations of [^{14}C]-lacosamide-derived radioactivity had the propensity to be associated with organs associated with metabolism and excretion and the lachrymal glands. At 0.5 hours after dosing, concentrations of radioactivity were below blood concentrations (12.6 µg eq/g for males and 12.8 µg eq/g for females) in all tissues with the exception of the stomach mucosa (77.3 µg eq/g for males and 86.1 µg eq/g for females), kidney medulla (19.1 µg eq/g for males and 18.5 µg eq/g for females), kidney inner cortex (15.4 µg eq/g for males and 16.9 µg eq/g females) kidney outer cortex (13.9 µg eq/g for males and 14.6 µg eq/g females), gall bladder

(18.2 µg eq/g for males and 19.6 µg eq/g for females), intra-orbital lachrymal gland (14.1 µg eq/g for males and 18.3 µg eq/g for females), female spleen (12.9 µg eq/g), female pancreas (13.3 µg eq/g), male seminal vesicle (13.2 µg eq/g) and male liver (12.7 µg eq/g).

- At one hour post-dosing, [^{14}C]-lacosamide-derived radioactivity concentrations in most tissues were at their maximum. Highest concentrations were determined in stomach mucosa (63.9 (male) and 24.9 µg eq/g (females)), kidney medulla (24.0 (males) and 18.0 µg eq/g (females)), intra-orbital lachrymal gland (23.9 (males) and 27.0 µg eq/g (females)) and exorbital lachrymal gland (23.8 (males) and 26.1 µg eq/g (females)).
- At 4 hours after dose administration, highest concentrations of [^{14}C]-lacosamide-derived radioactivity were determined in female gall bladder (53.6 µg eq/g), kidney inner cortex (17.3 and 18.0 µg eq/g in males and females, respectively), intra-orbital lachrymal gland (13.6 and 24.4 µg eq/g in males and females, respectively), kidney outer cortex (13.2 and 15.6 µg eq/g in males and females, respectively) and kidney medulla (13.6 and 14.7 µg eq/g in males and females respectively).
- At 8 hours post-dosing, highest concentrations of [^{14}C]-lacosamide-derived radioactivity were measured in kidney inner cortex (7.6 and 6.6 µg eq/g in males and females respectively) and in male kidney outer cortex (6.7 µg eq/g), male kidney medulla (7.9 µg eq/g), male stomach mucosa (7.23 µg eq/g), seminal vesicles (6.48 µg eq/g), female gall bladder (5.4 µg eq/g), female exorbital lachrymal gland (5.1 µg eq/g), female pancreas (5.4 µg eq/g) and male small intestine mucosa (4.2 µg eqs/g).
- At 24 hours after dose administration, highest concentrations of radioactivity were measured in the kidney inner cortex (3.1 and 3.3 µg eq/g in male and female respectively), seminal vesicles (3.1 µg eq/g) and female bone marrow (3.0 µg eq/g).
- At 72 hours post-dosing, concentrations of [^{14}C]-lacosamide-derived radioactivity were above the level of systemic exposure (concentration in blood; 0.4 (males) and 0.3 µg eq/g (females)) in most tissues. The highest concentrations of radioactivity were measured in kidney inner cortex (1.3 and 1.2 µg eq/g in male and female respectively), nasal mucosa (1.3 and 1.0 µg eq/g in males and females respectively) and bone marrow (1.3 and 0.7 µg eq/g in males and females respectively).
- The concentrations of [^{14}C]-lacosamide-derived radioactivity were below the systemic exposure up to 4 hours after dosing.
- Tissue concentrations of [^{14}C]-lacosamide-derived radioactivity were in general similar in male and female mice.
- There was no evidence that [^{14}C]-lacosamide was specifically binding to any tissue.

Tissue concentrations of [^{14}C]-lacosamide-derived radioactivity following a single oral administration of [^{14}C]-lacosamide to male and female mice at a dose level of 20 mg/kg.

		Concentration (µg equivalent (eq)/g)													
Tissue Type	Tissue/Organs	Males							Females						
		Time (hours)						% of C_{max} at 72 hrs	Time (hours)						% of C_{max} at 72 hrs
Vascular/Lymphatic		0.5	1	4	8	24	72		0.5	1	4	8	24	72	
	Blood	12.6	16.4	8.58	2.52	0.727	0.436	2.7	12.8	17.7	11.1	1.37	0.378	0.258	1.5
	Aorta	11.4	13.5	7.8	NS	0.945	0.509	3.8	10.9	12.8	7.65	1.59	0.702	0.415	3.2
	Mandibular lymph nodes	11.2	15.1	7.16	3.13	NS	0.764	5.1	NS	12.5	8.85	2.48	NS	NS	NA
Metabolic/excretory	Gall Bladder	18.2	NS	NS	4.56	0.549	NS	0.9	19.6	NS	53.6	5.41	0.224	0.180	0.3
	Kidney cortex (inner)	15.4	20.4	17.3	7.55	3.14	1.25	6.1	16.9	18.6	18.0	6.59	3.28	1.18	6.3
	Kidney cortex (outer)	13.9	18.2	13.2	6.69	2.24	0.989	5.4	14.6	16.7	15.6	4.11	1.52	0.622	3.7
	Kidney medulla	19.1	24.0	13.6	7.85	1.22	0.491	2.0	18.5	18.0	14.7	2.80	0.895	0.393	2.1
	Liver	12.7	15.9	10.2	4.19	1.38	0.567	3.6	11.4	15.9	12.3	3.05	1.32	0.535	3.4
CNS	Brain	7.23	10.7	5.08	1.95	0.611	0.234	2.2	6.88	8.25	6.56	1.13	0.371	0.166	2.0
	Pineal body	NS	NS	6.09	1.91	0.807	NS	NA	NS	NS	NS	NS	NS	0.116	NA
	Spinal cord	7.12	10.7	4.91	1.88	0.589	0.263	2.5	7.22	8.52	6.03	1.13	0.362	0.152	1.8
Endocrine	Adrenal	10.5	16.6	6.08	2.72	1.49	0.596	3.6	10.5	14.0	8.19	NS	1.57	0.389	2.8
	Pituitary	11.3	15.9	NS	3.55	1.56	NS	NA	11.6	14.5	10.6	2.27	1.61	0.582	4.0
	Thymus	10.2	14.7	8.16	3.14	1.31	0.651	4.4	9.28	12.8	9.08	2.30	1.43	0.585	4.6
	Thyroid	12.4	15.9	6.66	3.11	NS	NS	NA	NS	NS	6.03	2.52	NS	0.228	3.8
Secretory	Exorbital lachrymal gland	NS	23.8	14.9	4.32	0.949	0.415	1.7	NS	26.1	NS	5.06	1.08	0.327	1.3
	Harderian gland	9.39	13.6	5.88	3.22	1.61	0.676	5.0	9.03	12.7	13.8	2.14	1.57	0.633	4.6
	Intra-orbital lachrymal gland	14.1	23.9	13.6	3.96	0.840	0.607	2.5	12.1	15.7	14.5	3.29	0.945	0.396	1.4
	Salivary glands	12.0	17.2	9.35	4.04	1.37	0.633	3.7	12.1	15.7	14.5	3.29	0.945	0.396	2.5
Gonads (Males)	Epididymis	9.99	13.8	9.42	4.15	1.47	0.333	2.4	NA	NA	NA	NA	NA	NA	NA
	Preputial gland	7.83	11.1	4.93	1.04	0.811	0.363	3.3	NA	NA	NA	NA	NA	NA	NA
	Prostrate	NS	12.4	6.60	3.75	1.06	NS	NA	NA	NA	NA	NA	NA	NA	NA
	Seminal vesicles	13.2	NS	7.39	6.48	3.05	0.829	6.3	NA	NA	NA	NA	NA	NA	NA
	Testis	8.76	12.6	8.07	2.74	1.18	0.385	3.1	NA	NA	NA	NA	NA	NA	NA

	Concentration (µg equivalent (eq)/g)														
Tissue Type	**Tissue/Organs**	**Male**							**Female**						
		Time (hour)						**% of C_{max} at 72 hrs**	**Time (hour)**						**% of C_{max} at 72 hrs**
		0.5	**1**	**4**	**8**	**24**	**72**		**0.5**	**1**	**4**	**8**	**24**	**72**	
Gonads (Females)	Clitoris	NA	NA	NA	NA	NA	NA	NA	8.89	9.8	8.83	3.31	0.764	0.269	2.7
	Ovary	NA	NA	NA	NA	NA	NA	NA	12.0	12.3	9.24	2.50	1.48	0.455	3.7
	Uterus	NA	NA	NA	NA	NA	NA	NA	4.67	13.1	9.79	2.04	1.43	0.356	2.7
Muscular	Muscle	10.3	14.6	6.17	2.59	1.10	0.542	3.7	10.6	12.0	8.43	1.20	0.782	0.356	3.0
	Myocardium	11.7	15.6	6.90	2.88	0.993	0.560	3.6	11.4	13.3	9.80	1.32	0.858	0.389	2.9
	Tongue	11.9	16.2	7.51	3.01	1.01	0.516	3.2	11.0	13.0	8.93	1.85	0.789	0.367	2.8
	Lung	9.77	15.2	7.82	3.04	0.361	0.513	3.4	5.42	9.86	11.0	1.83	0.855	0.120	1.1
	Pancreas	12.2	15.3	10.5	5.25	1.91	0.582	3.8	13.3	15.5	12.1	5.35	1.32	0.378	2.4
	Spleen	12.0	15.3	9.26	4.46	2.14	0.647	4.2	12.9	16.7	12.2	3.33	1.72	0.607	3.6
	Stomach mucosa	77.3	63.9	10.8	7.23	1.36	0.655	0.8	86.1	24.9	10.2	4.77	1.57	0.458	0.5
	Small intestine mucosa	12.2	15.8	8.70	4.22	1.60	0.476	3.0	11.2	NS	8.31	3.96	2.05	0.451	4.0
	Cecum mucosa	9.99	6.92	6.41	BLQ	1.31	0.498	5.0	11.6	10.8	8.41	1.29	1.52	0.433	3.7
	Large intestine mucosa	11.1	16.0	7.52	5.28	1.25	0.538	3.4	7.27	14.0	11.9	3.13	1.75	0.335	2.4
	Rectum mucosa	12.0	14.3	6.86	2.75	NS	0.738	5.2	10.2	14.5	10.1	1.95	1.48	0.305	2.1
	Bone Marrow	10.9	14.0	7.43	3.45	2.31	1.31	9.4	10.3	11.9	10.8	3.79	3.04	0.702	5.9
	Non-pigmented skin	9.35	10.7	5.61	2.50	1.61	0.960	9.0	5.88	7.31	7.28	0.785	0.385	0.305	4.2
	Lens	0.658	3.05	2.92	4.13	1.52	0.222	5.4	1.26	1.15	7.86	2.13	0.844	0.072	0.9
	Ocular humor	6.18	6.24	3.31	1.53	0.378	0.186	3.0	4.21	7.16	4.81	0.753	0.400	0.105	1.5
	Uveal tract	8.14	8.89	4.67	1.92	0.622	0.220	2.5	8.87	9.95	7.72	1.04	0.422	0.251	2.5
Fatty	Brown fat	5.70	5.91	2.41	1.16	0.429	0.172	2.9	4.39	5.49	3.16	0.326	0.789	0.257	4.7
	White fat	3.00	3.63	0.771	0.229	0.206	0.128	3.5	1.88	2.61	1.61	0.190	0.120	0.099	3.8

b(4)

Study Title: Absorption, distribution, metabolism, and excretion of [^{14}C]-ADD 234037 in Sprague Dawley rats following either a single intravenous or oral administration.
Study №: F212

The distribution of [^{14}C]-lacosamide following either a single oral or intravenous dose of 10 mg/kg (3.7 MBq/kg) was characterized in male and female Sprague Dawley rats (IV: n=4/sex; PO: n=3). Lacosamide for intravenous and oral administrations were formulated in 0.15 M phosphate buffered saline and water, respectively. A single rat (1/gender) from the intravenous dosing group was euthanized and immediately frozen in a methanol/dry ice bath at 0.167, 0.5, 2 and 48 after dosing. Only male rats were evaluated following oral administration; one male was euthanized per time point (i.e., 1, 4, and 48 hours) following oral administration. All rats were prepared for whole-body autoradiography to qualitatively assess tissue distribution.

Key Study Findings:

- The distribution of radioactivity into tissues was similar following oral or intravenous administration of [^{14}C]-lacosamide.
- No organs showed excessive concentrations of radioactivity, preferential uptake or significant concentrations of [^{14}C]-lacosamide-derived radioactivity following either route of administration.
- No significant retention of [^{14}C]-lacosamide-derived radioactivity was detected at 48 hours post-dosing in any organs.
- At 0.167, 0.5 and 2 hours after intravenous administration, high levels of [^{14}C]-lacosamide-derived radioactivity were detected in
  - highly perfused organs/tissues: blood, lungs, heart, liver, spleen, skin, stomach, intestine (small and large), cecum, pancreas, and bone
  - glands: pituitary, thymus, harderian gland, submaxillary, and thyroid
  - organs involved in elimination: kidney, urine and bile duct.
- Following oral administration, the qualitative distribution of [^{14}C]-lacosamide-derived radioactivity was highest in tissues or organs of the digestive tract and organs involved in elimination. The esophagus, urine, urethra, bile duct, stomach content, and small intestine content at 1.0 hours after dosing. At four hours post-dosing, the highest concentration of [^{14}C]-lacosamide derived radioactivity was qualified in the: esophagus, stomach content, cecum content, small intestine content, corticomedulla junction of the kidney, urine and ureter.
- At one and four hours post dosing in males, high concentration of radioactivity was qualified in these tissues/organs:
  - One hour: blood, heart, kidney, liver, lung, spleen, skin, thymus, thyroid, submaxillary gland, pituitary, pancreas, bone marrow, muscle, cecum, large intestine, small intestine, stomach, testis, epididymis, seminal vesicles and urinary bladder.
  - 4 hour: blood, heart, kidney (cortex and medulla), liver, lung, spleen, skin, thymus, thyroid, submaxillary gland, pituitary, pancreas, bone marrow,

muscle, cecum, large intestine, small intestine, stomach, testis, epididymis, seminal vesicles and urinary bladder.
- Radioactivity levels were low in the bone marrow, seminal vesicles, thymus, kidney, spleen, small intestine, skin and ethmocurbinates 48-hours after oral dosing. Other tissues had no measurable levels of radioactivity.

Study Title: [^{14}C]-SPM 927: Quantitative whole-body autoradiography following oral and intravenous administration to the pigmented rat.
Study №: 0699/17

Tissue distribution of [^{14}C]-lacosamide following a single oral dose and single intravenous bolus of 10 mg/kg (61 MBeq/g) was characterized in male pigmented Lister Hooded rats. One rat from the oral dosing group was euthanized by being plunged into a freezing mixture following anesthesia under halothane at 1, 4, and 24 hours and at 2, 7, 14 and 35 days after dosing. A single rat from the intravenous dosing group was euthanized by being plunged into a freezing mixture following anesthesia under halothane at 10 minutes, 2, and 24 hours and at 2, 7, 14 and 35 days after dosing. Prior to anesthesia, blood was drawn from each rat and the level of radioactivity in plasma was measured. Concentrations of [^{14}C]-lacosamide in tissues were quantified from whole-body autoradiograms, using a radioluminography imaging system. Lower limit of quantification was 0.07 µg equivalents/g.

The table below show below shows the distribution of [^{14}C]-lacosamide-derived radioactivity in selected tissues (only tissue with large detectable amounts) following oral and intravenous administration.

Key Study Findings:
- The distribution of radioactivity into tissues was similar following oral or intravenous administration of [^{14}C]-lacosamide.
- No organs showed excessive concentrations, preferential uptake or significant concentrations of [^{14}C]-lacosamide-derived radioactivity following either route of administration.
- Concentrations of [^{14}C]-lacosamide-derived radioactivity was well distributed into tissues at the first sampling time (i.e., 1 hour) following oral administration.
- Concentrations of [^{14}C]-lacosamide-derived radioactivity were generally comparable for all tissues, at level similar to those measured in the plasma (approx. 9 µg equivalents/g plasma).
- The highest concentration of [^{14}C]-lacosamide-derived radioactivity was present in the coagulating glands (61.22 µg equiv/g).
- Radioactivity was detected in the central nervous system at a concentration that was half of that measured in the majority of other tissues.
- Following intravenous administration, [^{14}C]-lacosamide-derived radioactivity was widely distributed into tissues with peak concentrations at 10 minutes in

all tissues except the coagulating gland, uveal tract and the small intestine mucosa.

- Results obtained in pigmented skin and non-pigmented skin suggested that lacosamide does not bind significantly to melanin. The concentration of [^{14}C]-lacosamide-derived radioactivity was similar in both pigmented skin and non-pigmented skin at all sampling times. [^{14}C]-lacosamide-derived radioactivity was detected in the pigmented-containing tissues, uveal tract and pigmented skin, after both oral and intravenous administration. Also, the concentration of [^{14}C]-lacosamide in the uveal tract was comparable to other tissues.

Tissue concentrations of [^{14}C]-lacosamide-derived radioactivity following a single oral and intravenous dose of [^{14}C]-lacosamide to male pigmented Hooded rats at a dose level of 10 mg/kg.

	Concentration (µg equivalent (eq)/g)													
Tissue Type	**Tissue/Organs**	**Males (oral)**							**Males (intravenous)**					
		Time (hours)							**Time**	**Time (hours)**				
Vascular/Lymphatic		**1**	**4**	**24**	**48**	**168**	**336**	**840**	**10 min**	**2**	**24**	**48**	**168**	**336**	**840**
	Plasma	8.94	5.27	0.19	0.13	0.04	ND	ND	33.28	7.23	0.25	0.07	0.25	ND	ND
	Blood	9.31	5.11	0.31	0.22	0.14	BLQ	0.07	13.29	7.62	0.24	0.13	0.10	BLQ	BLQ
	Aorta	8.02	4.04	0.24	0.19	0.18	0.09	0.08	12.94	6.57	0.18	0.14	0.09	0.09	B;Q
	Mandibular lymph nodes	8.55	5.37	0.79	0.37	0.17	BLQ	BLQ	12.64	6.74	0.60	0.26	0.09	BLQ	BLQ
Metabolic/excretory	Kidney cortex	14,6	7.97	0.73	0.44	0.19	BLQ	BLQ	16.10	11.94	0.64	0.26	0.14	BLQ	BLQ
	Kidney medulla	13.59	6.65	0.49	0.32	0.15	BLQ	BLQ	16.23	10.11	0.46	0.26	0.17	BLQ	BLQ
	Liver	10.40	5.79	0.53	0.37	0.16	BLQ	BLQ	14.85	8.46	0.47	0.22	0.10	BLQ	BLQ
CNS	Brain	5.12	2.66	0.21	0.08	BLQ	BLQ	BLQ	7.95	3.92	0.12	BLQ	BLQ	BLQ	BLQ
	Pineal body	8.95	4.23	0.40	0.27	0.11	BLQ	BLQ	13.13	6.96	0.44	0.13	0.08	BLQ	BLQ
	Spinal cord	4.98	2.64	0.17	0.10	BLQ	BLQ	BLQ	6.81	3.59	0.17	BLQ	BLQ	BLQ	BLQ
Endocrine	Adrenal	8.89	4.91	0.53	0.40	0.168	BLQ	BLQ	13.78	7.55	0.48	0.24	0.11	BLQ	BLQ
	Pituitary	9.87	4.96	0.55	0.37	0.14	BLQ	BLQ	12.74	7.34	0.65	0.28	0.11	BLQ	BLQ
	Thymus	8.39	4.83	0.65	0.60	0.19	BLQ	BLQ	12.83	6.54	0.69	0.35	0.12	BLQ	BLQ
	Thyroid	8.42	4.72	0.51	0.43	0.20	0.11	BLQ	13.94	7.12	0.53	0.24	0.12	0.14	0.07
Secretory	Exorbital lachrymal gland	8.78	5.12	0.46	0.32	0.15	BLQ	BLQ	12.72	6.73	0.41	0.18	0.11	BLQ	BLQ
	Harderian gland	7.44	4.12	0.68	0.43	0.21	BLQ	BLQ	11.90	6.72	0.59	0.27	0.13	BLQ	BLQ
	Intra-orbital lachrymal gland	8.86	5.02	0.48	0.35	0.16	BLQ	BLQ	11.96	6.94	0.49	0.22	0.10	BLQ	BLQ
	Salivary glands	8.61	5.36	0.43	0.24	0.17	BLQ	BLQ	13.09	6.72	0.40	0.17	0.09	BLQ	BLQ
Gonads	Bulbo-urethal gland	8.96	5.09	0.46	0.36	0.39	NS	0.12	12.98	8.65	0.40	0.26	0.11	0.27	0.11
	Coagulating gland	61.22	25.8	2.15	0.50	0.55	BLQ	BLQ	12.57	55.34	0.55	0.27	0.17	BLQ	BLQ
	Epididymis	9.28	NS	0.45	0.20	0.10	BLQ	BLQ	10.41	8.10	0.42	0.14	0.09	BLQ	0.11
	Preputial gland	8.59	3.55	0.61	0.46	0.13	BLQ	0.13	12.38	6.31	0.44	0.28	0.09	BLQ	0.11
	Prostrate	8.37	4.47	0.59	0.55	0.12	BLQ	BLQ	13.77	13.28	0.56	0.29	0.09	BLQ	0.09
	Seminal vesicles	9.17	4.99	0.82	0.97	0.61	0.15	BLQ	13.68	7.66	1.41	0.54	0.33	0.10	BLQ
	Testis	7.84	4.66	0.46	0.24	0.13	BLQ	BLQ	7.58	7.39	0.33	0.18	0.07	BLQ	BLQ

BLQ: Below lower limit of qualification

	Concentration (μg equivalent (eq)/g)													
Tissue Type	**Tissue/Organs**	**Males (oral)**							**Males (intravenous)**					
		Time (hours)							**Time**	**Time (hours)**				
		1	**4**	**24**	**48**	**168**	**336**	**840**	**10 min**	**2**	**24**	**48**	**168**	**336**	**840**
Ocular	Lens	NS	1.63	0.93	0.22	0.30	BLQ	0.19	NS	6.64	0.52	0.31	BLQ	0.13	0.12
	Uveal tract	14.74	5.67	1.28	0.26	0.13	0.13	0.10	6.41	9.35	0.73	0.26	0.18	0.09	0.19
Muscle	Muscle	7.80	4.20	0.34	0.23	0.19	0.08	0.08	12.26	6.12	0.28	0.15	0.12	0.07	0.07
	Myocardium	8.71	4.80	0.41	0.29	0.20	0.07	BLQ	12.53	6.94	0.34	0.17	0.13	0.08	BLQ
	Tongue	8.57	4.35	0.42	0.29	0.16	BLQ	0.07	13.41	6.75	0.35	0.19	0.11	BLQ	0.07
Dermal	Non-pigmented skin	5.82	4.01	0.56	0.61	0.37	0.18	0.32	9.09	3.92	0.52	0.24	0.34	0.18	0.38
	Pigmented skin	5.95	3.95	0.46	0.61	0.34	0.28	0.26	9.62	4.43	0.49	0.27	0.24	0.18	0.27
Alomentary canal	Esophageal wall	9.38	5.88	0.95	0.91	0.44	BLQ	0.08	16.91	7.13	0.85	0.39	0.10	0.08	BLQ
	Stomach mucosa	10.4#	5.46	0.58	0.42	0.17	BLQ	BLQ	13.71	7.37	0.74	0.31	0.09	BLQ	BLQ
	Cecum mucosa	8.73	7.33#	NS	0.45	BLQ	BLQ	BLQ	13.84	6.63	1.01	0.32	0.07	BLQ	BLQ
	Large intestine mucosa	8.22	6.25	0.80	0.42	0.13	BLQ	BLQ	13.11	7.15	1.12	0.39	0.08	BLQ	BLQ
	Rectum mucosa	7.88	5.72	0.64	0.44	0.21	BLQ	BLQ	12.53	7.25	0.75	0.34	0.12	0.08	0.07
Others	Pancreas	9.49	6.03	0.71	0.31	0.14	BLQ	BLQ	12.61	7.11	0.59	0.24	0.14	BLQ	BLQ
	Spleen	9.52	5.28	0.77	0.52	0.22	BLQ	BLQ	13.30	7.30	0.76	0.32	0.14	BLQ	BLQ

BLQ: Below lower limit of qualification

#: Tissue measurement affected by flaring. Results reported are higher than the true value.

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Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog.
Study №: 0699/48

Tissue distribution of [^{14}C]-lacosamide was characterized in male (n=2) and female (n=2) Beagle dogs following a single oral dose of 10 mg/kg (4 MBq/kg). One male dog was euthanatized at 1, and 24 hour after oral dosing. One female dog was euthanatized at 4 and 48 hours after oral dosing. Tissues were analyzed for [^{14}C]-lacosamide radioactivity by direct liquid scintillation counting. The lower limit of quantification was 0.001 µg eq/g (pancreas) and 1.127 µg eq/g (pituitary gland). The table below shows the distribution of oral [^{14}C]-lacosamide in male and female dogs.

Key Study Findings:

- Radioactivity was widely distributed throughout the body from 1 hour to 48 hours with the maximum intensity at 1 hour. At this time, the highest levels of radioactivity were found in bile (40.86 µg eq/g), epididymis (20.03 µg eq/g), gall bladder (16.66 µg eq/g), kidney (17.64 µg eq/g), liver (12.74 µg eq/g), and urinary bladder (163.3 µg eq/g).
- Consistent with the distribution pattern observed in rodents, the highest concentrations of [^{14}C]-lacosamide-derived radioactivity was measured in organs of metabolism and excretion; the kidney, liver and gall bladder.
- Distribution of [^{14}C]-lacosamide-derived radioactivity were similar in male and females.

Tissue concentrations of [^{14}C]-lacosamide-derived radioactivity following a single oral administration of [^{14}C]-lacosamide to male and female dogs at a dose level of 100 mg/kg

	Concentration of [^{14}C]-lacosamide (µg eq/g)			
	Time (hour)			
Tissue/Organ	1 (Male)	4 (Female)	24 (Male)	48 (Male)
Blood	**7.967**	**3.623**	**0.125**	**0.044**
Adrenals	6.789	4.362	0.246	0.168
Aorta	6.947	5.887	0.254	BLOQ
Bile	**40.86**	**49.36**	**16.94**	0.845
Bone	1.564	0.707	0.115	0.101
Bone marrow	5.791	4.597	0.163	0.229
Cerebellum	5.770	3.052	0.284	0.117
Cerebrum	6.250	3.323	0.376	0.195
Epididymides	**20.03**	NA	0.370	NA
Eyes	4.329	4.185	0.315	0.112
Fat (Abdominal)	3.151	2.231	0.179	0.065
Gall bladder	**16.66**	**8.468**	**8.354**	0.574
Heart	7.919	4.913	0.237	0.147
Kidney	**17.64**	**11.48**	0.722	0.347
Large intestine plus contents	5.898	17.28	4.335	0.316
Liver	**12.740**	**8.598**	0.591	0.359
Lung	9.102	5.449	0.295	0.173

Mesenteric lymph nodes	7.623	4.816	0.275	0.191
Ovaries	NA	4.366	NA	0.076
Pancreas	8.509	4.750	0.475	0.070
Pituitary	**9.850**	**6.287**	0.315	0.165
Prostrate	8.546	NA	0.391	NA
Salivary gland	8.500	5.186	0.359	0.297
Seminal vesicles	7.165	NA	0.302	NA
Skeletal muscle (quadriceps)	8.022	3.637	0.332	0.227
Skin (non-pigmented	5.791	3.796	0.375	0.197
Skin (pigmented)	8.181	4.658	0.308	BLOQ
Small intestine plus contents	10.56	10.11	0.492	0.201
Spinal cord	4.919	2.747	0.258	0.081
Spleen	8.405	4.689	0.284	0.159
Stomach plus contents	5.458	3.783	0.312	0.137
Testes	8.799	NA	0.336	NA
Thymus	4.004	4.183	0.296	0.190
Thyroid	7.712	4.762	0.287	0.199
Trachea	5.884	3.765	0.203	BLOQ
Urinary bladder plus contents	**163.3**	**317.3**	7.767	0.645
Uterus	NA	**6.101**	NA	0.158
% of dose	**23.42**	**20.24**	**2.398**	**0.333**

BLOQ (below the level of quantitation)

Study Title: [^{14}C]-SPM 927: Placental transfer, lacteal secretion and transfer to suckling neonates in the rat
Study №: 699/15

The objective of this study was to use whole body autoradiography to quantitate the distribution of [^{14}C]-lacosamide in pregnant rats, and suckling rat neonates; and to characterize the distribution in lacteal secretion.

Three groups of Sprague Dawley rats were subjects for this study. In the first group of rats, placental transfer was evaluated in pregnant rats (day 18 of gestation when dosed; n = 3) after a single oral dose of 10 mg/kg (6.5 MBq/kg) [^{14}C]-lacosamide. A single pregnant rat was anaesthetized under halothane rat and immediately euthanized by being plunged into freezing mixture of dry ice and hexane at 4, 12, and 24 hours after dosing, Immediately prior to anesthesia blood was drawn. Level of radioactivity in plasma was measured by liquid scintillation. The lower limit of quantification for lacosamide was 0.007 µg eq/g of tissue. Concentration of [^{14}C]-lacosamide in tissues were quantified from whole-body autoradiograms using a validated image analysis system.

In the second group of rats, suckling dams (on day 10 post-partum when dosed; n = 3) were used to assess the distribution of [^{14}C]-lacosamide-derived radioactivity into milk after a single oral dose of 10 mg/kg (6.5 MBq/kg) [^{14}C]-lacosamide. Samples of milk and plasma were collected from these suckling dams at 30 minutes, 1, 2, 4, 8 and 24 hours after dosing. The radioactivity in milk and plasma were determined by liquid scintillation.

In the third group, suckling dams (n = 3) were used to measure the distribution of [^{14}C]-lacosamide-derived radioactivity in neonates. Pregnant Sprague Dawley rats were allowed to produce a litter. On day 10 post-partum, they received a single oral dose of

[^{14}C]-lacosamide (10 mg/kg). The number of neonates in each litter was reduced to 8. Three neonates were analyzed at 4 and 24 hours post-dosing. Tissue distribution in suckling rats was quantified by whole-body autoradiography. The lower limit of quantification for lacosamide was 0.007 or 0.13 µg eq/g.

Key Study Findings:

- Radioactivity was widely distributed into maternal tissues following a single oral dose of [^{14}C]-lacosamide. Peak concentrations of [^{14}C]-lacosamide-derived radioactivity occurred at the first sampling time (4 hours) in all tissues and there after declined slowly. Concentrations of [^{14}C]-lacosamide-derived radioactivity was still measurable at 24 hours after dosing.
- At 4 hours, all maternal tissues measured contained quantifiable radioactivity; concentrations of [^{14}C]-lacosamide-derived radioactivity was comparable to the concentration of radioactivity measured in the plasma (5.57 µg eq/g). The maternal tissues with concentrations greater than 1.5 times that in the plasma were the kidney cortex, kidney medulla, and mucosa of the caecum. According to the Sponsor, due to flaring, the actual level should be lower for the caecum mucosal. Maternal tissues containing the lowest concentrations of radioactivity (below 1 µg eq/g) included the white fat, bone and the nasal mucosa.
- At 12 hours after dosing, radioactivity concentrations in the maternal tissues had declined but all tissues sectioned still contained quantifiable levels of [^{14}C]-lacosamide-derived radioactivity. Most tissues contained concentrations of radioactivity similar to that in plasma (1.86 µg eq/g). The highest levels of [^{14}C]-lacosamide-derived radioactivity were measured in the bone marrow (3.63 µg eq/g) kidney cortex (2.69 µg eq/g), intra-orbital lachrymal gland (2.76 µg eq/g), pancreas (2.50 µg eq/g), spleen (2.92 µg eq/g)and the small intestine mucosa (2.70 µg eq/g). Lowest concentrations of radioactivity (below 1 µg eq/g) were measured in the brain (0.81 µg eq/g), spinal cord (0.74 µg eq/g), brown (0.75 µg eq/g) and white fat (0.28 µg eq/g), bone (0.19 µg eq/g) and the nasal mucosa. (0.14 µg eq/g).
- [^{14}C]-Lacosamide-derived radioactivity readily crossed the placental barrier. Concentrations of radioactivity in fetal tissues were mostly comparable with the corresponding tissues in the dams with the exception of the brain and kidney. The radioactivity concentration in the fetal brain was higher than in the dam; whereas, the radioactivity concentration in the fetal kidney was lower than in the dam.
- Suckling neonates were exposed to radioactivity with a distribution similar to that of the maternal tissues in pregnant rats. Radioactivity was widely distributed in the tissues of the neonates at 4 hours after dosing. Also, tissue concentrations of [^{14}C]-lacosamide-derived radioactivity were generally similar for all neonate sampled from a single dam. At 24 hours following dosing, concentrations of [^{14}C]-lacosamide-derived radioactivity in neonatal tissues were generally higher than at 4 hours. Compared to the 4 hours time point, the concentrations of radioactivity measured in the tissues at 24 hours

were more comparable between neonates from different dams. Highest concentrations of radioactivity were associated with the mucosa of the gastrointestinal tract. The lowest levels were measured in the brain, spinal cord and nasal mucosa. Detection of radioactivity in the contents of the gastrointestinal and renal tracts indicated that these were possible routes of elimination.

- Radioactivity was detected in the milk at all sampling times after the oral administration of [^{14}C]-lacosamide to suckling dams. Concentrations increased up to 2 hours post-dose and then declined. Concentrations of [^{14}C]-lacosamide-derived radioactivity in milk increased from 4.81 µg eq/g at 30 minutes after dosing to 7.87 µg eq/g 2 hours after dosing. Detectable radioactivity was still present 24 hours after dosing. The ratio of radioactivity in the milk relative to the plasma increased from 0.73 at 30 minutes after dosing to 2.45 at 8 hours. At 24 hours after dosing, this ratio had decline to 0.89.

Concentrations of radioactivity in select tissues of pregnant Sprague Dawley rats (in day 18 of gestation at dosing after a single oral administration of [^{14}C]-lacosamide (10 mg/kg)

	Concentration of [^{14}C]-lacosamide-derived radioactivity (µg eq/g)			
		Time (hour)		
Tissue Type	**Tissue/Organ**	**4**	**12**	**24**
Dams				
	Blood	**5.57**	**1.86**	**0.30**
Tissues with concentrations that was greater than 1.5 times that of the plasma at the first sampling time				
Metabolic/Excretatory	Kidney Cortex	9.04	2.69	0.62
	Kidney Medulla	9.34	5.887	
Alimentary Canal	Cecum mucosa	12.23#	2.38	1.05
Tissues with the lowest concentrations (less than 1 µg eq/g) of radioactivity at the first sampling time				
Fatty	White fat	0.86	0.28	0.10
Skeletal	Bone	0.37	0.19	0.11
Other	Nasal mucosa	0.65	0.14	0.13
Gonads	Uterus	6.46	2.27	0.72
Unclassified	Pancreas	6.75	2.60	0.55
	Spleen	6.32	2.92	1.12
Alimentary Canal	Esophagus wall	6.66	1.67	0.34
	Large intestine plus mucosa	5.67	2.14#	0.83
	Stomach mucosa	6.53#	2.70	1.25
	Small intestine mucosa	7.71#	2.70	1.25

Concentrations of radioactivity in fetal tissues of pregnant Sprague Dawley rats (in day 18 of gestation at dosing) after a single oral administration of [^{14}C]-lacosamide at a dose of 10 mg/kg.

	Concentration of [^{14}C]-lacosamide-derived radioactivity (µg eq/g)					
	Time (hours)					
Tissue/Organ	4 (Fetus)	4 (Dam)	12 (Fetus)	12 (Dam)	24 (Fetus)	24 (Dam)
Placental	5.82	5.82	1.97	1.97	0.53	0.53
Blood	7.30	5.78	2.15	1.71	0.84	0.27
Adrenals	5.41	5.85	2.18	2.23	0.78	0.49
Brain	4.99	2.76	1.76	0.81	0.66	0.13
Eye	6.40	1.13 (Lens)	2.70	NS	1.15	NS
Heart	5.03	5.44	2.07	1.55	0.86	0.37
Kidney	5.65	Cortex: 9.04 Medulla: 9.34	2.41	Cortex: 2.69 Medulla: 2.31	0.90	Cortex: 0.62 Medulla: 0.46
Liver	5.62	6.20	2.90	2.24	0.96	0.60
Lung	5.47	4.59	2.36	1.66	0.79	0.35
Skin	7.85	3.42	1.81	1.09	0.57	0.15

Table (Table 4 of Sponsor's submission). Concentrations of radioactivity in milk and plasma following a single oral administration of [^{14}C]-lacosamide to rats on day 10 *post-partum* at a nominal dose level of 10 mg/kg body weight

Animal number and sex	Sampling time	Radioactivity concentration (µg equiv/g)		Milk/plasma ratio
		Milk	Plasma	
		Mean	Mean	Mean
170F 171F 172F	30 min	4.81	6.62	0.73
156F 167F 173F	1 h	7.05	8.55	0.83
159F 162F 163F	2 h	7.87	6.66	1.18
153F 158F 168F	4 h	7.84	5.32	1.47
152F 157F 164F	8 h	3.61	1.54	2.45
1F 2F 9F	24 h	0.31	0.34	0.89

b(4)

Study Title: [^{14}C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat
Study №: 699/23

The objective of this study was to determine the distribution of [^{14}C]-lacosamide-derived radioactivity in the brain following single oral administration in Sprague Dawley rats. Male Sprague Dawley rats (n=6) were administered a single oral dose (10 mg/kg, 5.0 MBq/kg) of [^{14}C]-lacosamide formulated in sterile deionised water at 2 mg/mL. At 1,

1.5, 6 and 24 hours post-dosing, two animals were evaluated per time point. Blood samples were collected at the same time points. Radioactivity levels in plasma were measured using liquid scintillation counting. Concentrations of [^{14}C]-lacosamide-derived radioactivity in brain were quantified from whole-body autoradiograms, using a radioluminography imaging system. Lower limit of quantification was 0.091 µg equiv/g.

Key Study Findings:

Concentration of [^{14}C]-lacosamide-derived radioactivity in brain and plasma following a single oral administration of [^{14}C]-lacosamide (10 mg/kg).

	Concentration [µg eq/g]		
Tissue	1.5 hours	6 hours	24 hours
Plasma	6.89	3.51	0.38
4th ventricle	NSV	1.66[a]	NSV
Caudate putamen	3.02	1.33	NSV
Corpus callosum	2.72	1.29	NSV
Dentate gyrus	2.99[a]	NSV	NSV
Dorsal 3rd ventricle	3.79	1.96	NSV
Forceps major corpus callosum	2.26[a]	1.41[a]	NSV
Hippocampus	3.15	1.30	NSV
Lateral ventricle	3.50	1.82[a]	NSV
Motor cortex	1.28[a]	NSV	NSV
Periaqueductual grey	2.23[a]	NSV	NSV

NSV: Not specifically visible

- As depicted in the table above (as copied from the Sponsor's submission), highest concentration of [^{14}C]-lacosamide-derived radioactivity were associated with all regions of the brain at 1.5 hours after dosing. The mean concentration of radioactivity for the brain as a whole was 3.1 µg equiv/g and was lower than levels of radioactivity in plasma (6.89 µg equiv/g)
- At 1.5 hours post-dosing, the caudate putamen (3.02 µg equiv/g), dentate gyrus (2.99 µg equiv/g) and hippocampus (3.15 µg equiv/g) contained similar levels of [^{14}C]-lacosamide-derived radioactivity. The highest level of radioactivity was measured in the dorsal third ventricle and lateral ventricle, 3.79 and 3.50 µg equiv/g, respectively.
- The lowest level of radioactivity at 1.5 hours were measured in the corpus callosum (2.72 µg equiv/g), forceps major of the corpus callosum (2.26 µg equiv/g), periaqueductal gray (2.23 µg equiv/g) and motor cortex (1.28 µg equiv/g).
- Six hours after dosing, the levels of [^{14}C]-lacosamide-derived radioactivity were much reduced in all brain regions.
- By 24 hours post-dosing, levels of radioactivity in the brain had declined significantly. The mean measurement for all regions of the brain was 0.26 µg equiv/g and was lower than the levels of radioactivity in plasma (0.38 µg equiv/g).

2.6.4.5 Metabolism

The metabolism of lacosamide was characterized in both in vivo and in vitro studies. In vitro metabolism of lacosamide was investigated in liver microsomes (rat, dog, monkey and human), hepatocytes (mouse, rat, rabbit, dog and human) and kidney microsomes (rat

and human). The in vivo biotransformation of lacosamide was characterized following oral or intravenous administration in rat, mouse and dog.

Study Title: <u>In vitro metabolism of ADD 234037 using liver microsomes from rat, dog, monkey and human.</u>
Study №: 9818851

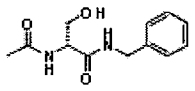
Pooled liver microsomes from Sprague Dawley rats, dog (Beagle), cynomolus monkeys and humans were incubated with lacosamide (ADD 234037) at a concentration of 100 µmol/L (25 µg/mL) for 15, 30 and 60 minutes. Three control incubations were conducted: 1) without the NADPH co-factor for involvement of cytochrome P450 activity, 2) with substrate (negative control), without lacosamide substrate (i.e, microsomes). Chemical structures of the metabolites were examined with LC-MS/MS.

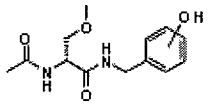
Key Study Findings:

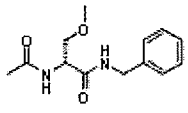
- No significant metabolism occurred when lacosamide was incubated with microsomes in the absence of NADPH.
- Results suggest that cytochrome P450 enzymes play a minor role in the hepatic clearance of lacosamide. In the presence of NADPH, two minor metabolites were identified in rat, dog and monkey liver microsomes after 60 minutes of incubation. Lacosamide underwent biotransformation to both phenolic (M2) and desmethylated (M1; hydroxylation of the methoxy moiety) metabolites.
- No biotransformation of lacosamide was exhibited in human's liver microsomes; only the parent compound was identified.

		Metabolite Profiling			
	Identification	**Rat**	**Dog**	**Monkey**	**Human**
M1	O-demethylated metabolite	Minor	Minor	Minor	-
M2	Monohydroxylated Metabolite	Minor	Minor	Minor	-
Lacosamide	Parent	Major	Major	Major	Major

- Proposed Structures:

M1 

M2 

ADD 234037 (Lacosamide) 

Study Title: [^{14}C]-SPM 927: Metabolism in hepatocytes isolated from mouse, rat, rabbit, dog and man

Study №: 0699/25

The objective of this study was to identify and compare the number and proportions of metabolites produced when liver hepatocytes isolated from mouse, rat, rabbit, dog and human are incubated with [^{14}C]-lacosamide. Suspension cultures of fresh hepatocytes isolated from the livers of male Sprague Dawley rats, male CD-1 mice, female New Zealand rabbit, male dog (Beagle), and humans (2 male donors) were incubated with [^{14}C]-lacosamide at a concentration of 10 µmol/L (2.5 µg/mL) for 2 and 4 hours 15, 30 and 60 minutes. To determine if conjugates are formed, the metabolism of lacosamide was evaluated in the presence of β-glucuronidase/aryl suphatase or sulphatase-free β-glucuronidase. Concentrations of metabolites were determined by LC-MS/MS and HPLC (radio and UV-detection) methods.

Key Study Findings:

- Metabolic turnover was low in rabbit, dog and human hepatocytes.
- Metabolic turnover was high in mouse and rat hepatocytes.
- After 4 hour incubation, on average 55%, 22%, 7%, 15% and 4% of lacosamide had been metabolized by mouse, rat, rabbit, dog and human hepatocytes, respectively.
- Three metabolites were detected following incubation of fresh hepatocytes with [^{14}C]-lacosamide. They consisted of a desmethyl metabolite (M1, SPM 12809), a p-hydroxy metabolite (p-M2, SPM 12817), and a desacyl metabolite (M5, SPM 6912). Two unknown metabolites were also identified.
- The desmethyl metabolite, SPM 12809, was common to all species.
- The two major metabolites detected in rat, rabbit and dog were identified as the p-hydroxy metabolite and desmethyl metabolite.
- Qualitatively, the metabolic profile of lacosamide in hepatocytes from human only resembled mouse.
- The metabolite profile observed across species is tabulated below.

	Metabolite Profiling						
	% of Compound in Sample						
		M1: SPM 12809	p-M2: SPM 12817	M5: SPM 6912	Unknown 1	Unknown 2	Lacosamide
Species	Time						
Mouse	0	-	-	-	0.5	-	99.6
	2	3.9	-	25.8	4.4	-	65.9
	4	4.6	-	41.6	6.8	-	45.3
Rat	0	-	-	-	-	-	100
	2	3.4	3.4	-	2.4	2.9	87.9
	4	6.7	6.7	-	3.0	5.8	77.8
Rabbit	0	-	-	-	-	-	100
	2	2.3	0.5	-	1.4	-	95.4
	4	4.3	1.0	-	2.1	-	92.7
	0	-	-	-	1.2	-	98.8

Dog	2	2.9	1.4	-	1.7	-	93.2
	4	7.3	3.7	-	2.5	-	85.2
Human Donor 1	0	-	-	-	1.3	-	98.8
	2	0.2	-	-	1.8	-	98.2
	4	0.3	-	-	21.9	-	97.9
Human Donor 2	0	-	-	-	1.3	-	98.6
	2	0.4	-	0.2	1.9	-	97.6
	4	0.6	-	0.7	2.4	-	96.3
	6	0.7	-	0.9	2.3	-	96.2
	10	1.3	-	1.8	2.6	-	94.4

Study Title: Investigation of the metabolism of SPM 927 in different in vitro models
Study №: 0688

The objective of this study was to identify enzymes involved in the metabolism of [^{14}C]-lacosamide in liver and kidney microsomes obtained from the rat and human liver and kidney microsomes supernatant from the rat and human plasma and microsomes obtained from baculovirus infected insect cells transfected with human cytochrome P450 2C19 cDNA. —— b(4)

Methodology as copied from the Sponsor's submission: "The metabolism of [^{14}C]-lacosamide was determined at ca. 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]-lacosamide was 100 µM. CYP2C19 —— were additionally incubated with 10 µM [^{14}C]-lacosamide. 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]-lacosamide, incubations were performed without the NADPH regenerating system. Additionally, the influence of flavin monooxigenase (FMO) enzymes was investigated."

Key Study Findings:

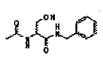
- In the in vitro rat model, 4 metabolites of lacosamide were identified. SPM 12809 (M1) and SPM 12817 (p-M2) accounted for 4.9% and 2.69% of the total radioactivity in the chromatogram analyzed in the liver microsomes, respectively. Traces of SPM 6923 (M5), unknown 3, SPM 12813 (m-M3) and unknown 1 were observed in liver microsomes. In the liver supernatant unknown metabolites 1, 2 and 3 were identified. In addition, trace amount of SPM 6912 (M5) was found in liver and kidney supernatant and microsomes.
- In the human in vitro model, 3 significant metabolites were observed in liver microsomes; SPM 12809 and SPM 6912. SPM 12809 and SPM 6912 accounted for 2.5% and 1.4% of the compounds identified in the liver microsomes, respectively.
- Results from the human in vitro assay using human CYP2C19 suggest that CYP2C19 is involved in the formation of SPM 12809. Two significant metabolites were observed; SPM 12808 (6.88%) and an unknown polar metabolite (7.68%).

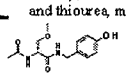
b(4)

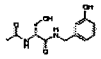
The following table submitted by the Sponsor provides a species comparison of the presence of metabolites of lacosamide in microsomes or microsomal supernatant:

Compound	RT [min]	% of compound in sample after 24 hours incubation																	
		Rat liver				Rat kidney				Human liver			Human kidney			Human CYP2C19			
		Microsomes NADPH		Supernatant NADPH		Microsomes NADPH		Supernatant NADPH		Microsomes pH			Microsomes pH			100 µmol/L NADPH		10 µmol/L NADPH	
		yes	no	yes	no	yes	no	yes	no	7.4	9.5-A	9.5-B	7.4	9.5-A	9.5-B	yes	no	yes	yes-48 h
Unknown 1	1.5	+	-	1.50	1.64	+	+	1.51	1.39	+	-	-	+	-	-	-	-	+	-
Unknown 2	2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1.65	7.68
Unknown 3	2.5	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	-
m-M3	9.5	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
p-M2	11	2.69	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
M5	12.5	+	+	-	+	-	+	-	+	1.40	+	+	-	-	-	-	-	-	-
M1	13	4.87	-	-	-	-	-	-	-	2.46	+	+	+	-	-	1.28	-	6.27	6.88
Lacosamide	17	89.9	99.1	97.8	97.2	98.9	98.7	98.1	98.1	94.5	99.0	99.3	98.3	99.3	99.7	98.1	99.0	92.0	90.8

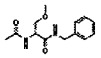
Additional information: Data are given as median (samples were measured in duplicate); n = 1 (rat liver microsomes) or a pool of 5 (rat and human kidney microsomes) or 30 donors (human liver microsomes); + = >0.1 and < 1.0% total radioactivity, - = no peak identified
A = with —— , B = with —— and thiourea, m = meta, p = para, RT = retention time


M1 = SPM 12809
(O-desmethyl metabolite)


p-M2 = SPM 12817
(p-hydroxy metabolite)


m-M3 = SPM 12813
(O-desmethyl m-hydroxy metabolite)


M5 = SPM 6912
(desacetyl metabolite)


Lacosamide

b(4)

Study Title: SPM 927: Metabolite profiling and identification in the mouse, rat and dog.
Study №: 826

The objective of the study was to identify the major metabolites of lacosamide in plasma, urine and feces extract samples obtained from male and female mice, rats and dogs in other toxicology studies —— study numbers 699/46, 699/47 and 699/48). Metabolite profiling was done with radio-HPLC and mass spectrometry.

Key Study Findings:

- Metabolite profiling indicated the presence of several metabolites in plasma, urine and feces. In plasma, urine and feces, a total of 17, 25, and 24 metabolites, respectively, were detected across all species.
- No major difference relating to route of metabolism was observed between genders across species.
- Identification of major metabolites in plasma is listed in the Sponsor's table below. The parent compound, lacosamide, accounted for 72.5%, 70% and 88.5% of the radioactivity in mice, rat and dog plasma, respectively. In all three species, the O-demethylated metabolite (SPM 12809) was the major metabolite. SPM 12809 accounted for 17.2% (male) and 22.0% (female), 15.45% (male) and 17.1% (female) and 33.4% (male) and 36.2% (female), in mice, rat and dog, respectively. The para-hydroxy metabolite SPM 12817 was present in all three species plasma; it accounted for a small percentage (2.27% to 7.73%) of the radiaoctivity. In mice, another major compound identified as an un-identifiable polar peak represented 27% of the radioactivity.

Major plasma metabolites following single oral administration of [^{14}C]-lacosamide

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

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

- **Urine.** In urine, a total of 25 metabolites were detected across all species. Identification of major metabolites in urine is listed in the Sponsor's table below. In mice, 53% (mean) of the dosed radioactivity was measured in urine. The O-demethylated metabolite SPM 12809 and parent compound lacosamide represented 34.5% (mean) and 33% (mean) of the recovered radioactivity, respectively. Minor metabolites represented the remaining recovered radioactivity. Minor urinary metabolites included SPM 6912, glucurinide conjugates of meta-hydroxy, the O-desmethyl, the O-methoxy and the N-carbamoyl metabolites. In rats, 75.4% (mean) of the dosed radioactivity was measured in urine. The parent compound represented 25.1% (mean) of the total radioactivity recovered. SPM 12809 was the major metabolite identified in rat urine; representing 41.8% (mean) of the recovered radioactivity. Minor metabolites in rat urine were SPM 12817 (2.5% (mean)), SPM 12814, M6 (0.9% (mean)). Consistent with rats and mice, SPM 12809 was identified as the major urinary metabolite in dogs; representing 41% (mean) of the total recovered radioactivity. The parent compound lacosamide represented 9% (mean) of the total radioactivity. Minor metabolites identified were para-hydroxylated metabolite (SPM 12817), SPM 12814 and glucuronide conjugate of the meta-hydroxy, O-desmethyl, the O-methoxy and the N-carbamoyl metabolites.

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Major metabolites in urine following single oral administration of [^{14}C]-lacosamide

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

Data presented are after single oral administration [^{14}C]-lacosamide at 20 (mice), 40 (rats) and 10 mg/kg (dogs). Pooled urine samples (0-24 hours) were investigated by radioHPLC-MS/MS

a - Investigations with [^{14}C] lacosamide labeled either at the carboxylic or at the benzylic carbon atom suggest the formation of a desbenzylamine derivative (4.2.2.4.6, 847).

b - When employing the HPLC method which was used for human urine from trial SP619, the 6- and 8-minute peaks co-eluted as one peak at a retention time of 1.6 minutes (4.2.2.1, 1000)

BLQ = below the limit of quantification (0.15 - 0.63% of the dose), - = not detected

- **Feces.** In male mice, 4.6% of the dosed radioactivity was observed in feces. The parent compound lacosamide accounted for 28.7% of the excreted radioactivity. SPM 12809 accounted for up to 4.34%. The deacetylated metabolite SPM 6912 was identified as a minor metabolite that was detected in trace amounts. In rats, 5.3% of the dosed radioactivity was recovered in feces. The O-demethylated metabolite SPM 12809 was the major metabolite identified in feces; representing 17.8% of the recovered metabolite. The para-hydroxylated metabolite (SPM 12817) represented 14.6% of the recovered radioactivity. Lacosamide represented 29.3% of the recovered radioactivity. The rest of the radioactivity was accounted for by 18 other minor metabolites. In dogs, 5.4% of the radioactivity metabolites identified was in feces. Approximately 14%, 16% and 39% of the recovered radioactivity was identified as lacosamide, SPM 12809 and SPM 12817, respectively. Fifteen other metabolites represented the remaining drug-related radioactivity.
- The Sponsor proposed metabolic pathway for lacosamide in mice, rat and dog is presented below (copied from Sponsor's submission).

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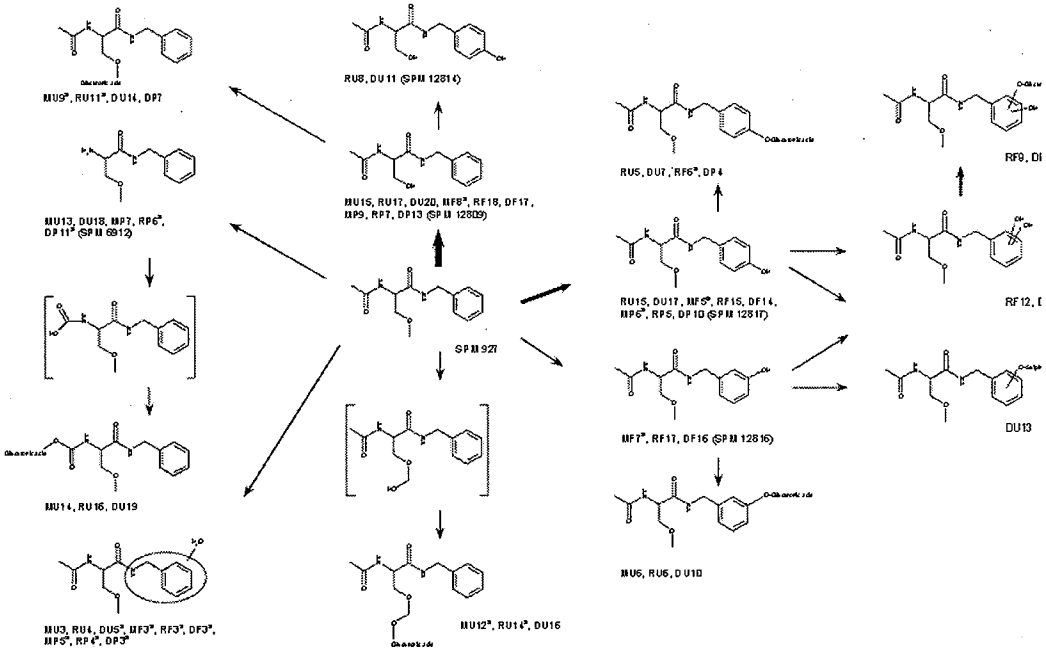
Proposed metabolic pathway of SPM 927 after administration to mice, rats and dogs



The structure in brackets was not observed
a: found in profiling samples only, LC-MS/MS data could not be obtained

Study Title: <u>Investigation of the Cytochrome P540 1A2 and 3A4 induction of the compound SPM 927 in cryopreserved human monocytes</u>.
Study №: BA 555-02

The induction potential of the cytochrome P450 isoforms CYP1A2 and CYP3A4 by lacosamide was investigated in cryopreserved human hepatocytes. Cryoperserved human hepatocytes from 2 female donors were incubated for 72 hours with 50 and 500 µM of lacosamide. Positive controls were β-naphthoflavone, dexamethasone and rifampicin. DMSO and acetonitrile were the vehicles used for the assays.

Key Study Findings:

- As depicted in the Sponsor's table below, lacosamide showed no potential to induce the activity of CYP1A2 at either concentration.
- At 50 µM lacosamide did not induce CYP3A4. In contrast, at a concentration of 500 µM lacosamide, a slight induction of CYP3A4 was observed in one of the two donors examined in the presence of acetonitrile as vehicle.

Tabulated results:

Solvent	Donor	Induction factor for CYP1A2				Induction factor for CYP3A4				
		Solvent control	β-Naphthoflavone 50 µmol/L	Lacosamide 50 µmol/L	Lacosamide 500 µmol/L	Solvent control	Dexamethasone 50 µmol/L	Rifampicin 50 µmol/L	Lacosamide 50 µmol/L	Lacosamide 500 µmol/L
1% DMSO	1	1.0	2.2	0.5	0.4	1.0	1.5	2.3	-	1.4
	2	1.0	17.8	0.6	0.8	1.0	1.1	3.3	-	1.2
1% Acetonitrile	1	1.0	1.4	0.8	0.9	1.0	1.2	3.2	1.0	1.0
	2	1.0	20.9	0.6	0.6	1.0	3.0	11.0	1.2	1.7

Additional information:
The induction factor was calculated as ratio of metabolite in sample or solvent control versus metabolite in solvent control.
- = experimental error, calculation not reasonable
DMSO = dimethylsulfoxide, EROD = ethoxyresorufin-O-deethylation

Study Title: Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes.
Study №: 732

The objective of this study was to investigate the cytochrome P450 induction potential of lacosamide in human hepatocytes obtained from male and female donors. The potential of lacosamide to induce the cytochrome P450 isoforms 1A2, 2B6, 2C9, 2C19 and 3A4 were examined in cryopreserved human hepatocytes at 50 and 500 µmol/L. Analysis of enzyme activities was done by fluorimetry or by HPLC with UV detection or radio detection.

Key Study Findings:

- The Sponsor's tabulated results are presented in the table below. At therapeutic concentrations (50 µmol/L = 12.5 µg/mL), lacosamide did not induce any of the tested cytochrome P450 enzymes.
- In two of the three donors, enzyme activities were less than 2-fold those of non-treated hepatocytes after treatment with 500 µmol/L of lacosamide. In one donor, enzyme activities of CYP3A4 were three times higher than the solvent treated group but less than 0.2 times lower than the positive induced control group. The Sponsor does not consider this as relevant since it accounts for only 20% of the activity determined in the positive control. To support their conclusion, the Sponsor stated that "According to Bjornsson et al. an induction at 40% of the positive control induction level would indicate a positive inductive response (Bjornsson et al., 2003)."

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Tabulated results:

CYP450 isoform	Donor	Substrate [µmol/L]	Control inducer Compound [µmol/L]	Control inducer % of control	Lacosamide, 50 µmol/L % of control	Lacosamide, 500 µmol/L % of control
CYP1A2	/	7-Ethoxyresorufin [7.5]	Omeprazole [100]	633	96.8	102
	/			536	86.0	91.4
	417			258	93.1	93.7
	— —	Phenacetin [100]	Omeprazole [100]	2988	92.9	104
	/			1835	90.1	98.0
	417			822	100	115
CYP2B6	/	(S)-Mephenytoin [100]	Phenobarbital [200]	490	93.3	88.5
	/			536	89.0	148
	417			220	93.4	129
CYP2C9	/	(S)-Warfarin [10]	Rifampicin [20]	333	110	180
	417			219	112	110
CYP2C19	/	(S)-Mephenytoin [100]	Rifampicin [20]	215	98.0	74.6
	/			216	73.6	61.4
CYP3A4	/	Testosterone [250]	Rifampicin [20]	2018	103	131
	/			1921	161	323
	417			> 934	NA	NA

Additional information:
Induction was considered positive at more than 200% and negative at less than 50% of enzymatic activities of control.
Gender of donors: 417 male — and — female
NA = not applicable

Study Title: Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes
Study №: NO1-NS-4-2311

The potential induction effects of lacosamide were studied in male Sprague Dawley rats. The rats (n = 8/group) were orally dosed with vehicle, 3, 9 or 100 mg/kg of lacosamide up to seven days. On days 8 and 9, 4 rats from each group were euthanized. Protein concentrations and enzyme activities were analyzed in liver microsomes and the cytosol fraction. Enzyme activities were analyzed by reverse-phase HPLC.

Key Study Findings:

- Lacosamide did not induce an increase in overall cytochrome P450 concentrations; CYP1A or CYP2B activity.

Study Title: An investigation of the potential for harkoseride to inhibit cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.
Study №: M1999-057

The objective of this study was to evaluate potential inhibitory effects of lacosamide on the human liver cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Cryopreserved human hepatocytes were incubated with 100 µmol/L (25 µg/mL). The activity of each enzyme was determined in the hepatocytes in the presence and absence of each test article and positive control inhibitor.

Key Study Findings:

- The Sponsor's tabulated results are presented in the table below.
- With the exception of CYP2C19, lacosamide showed no potential to inhibit enzyme activity of CYP isoforms in human hepatocytes under the experimental conditions.

- Lacosamide, at 100 µM concentration, significantly inhibited CYP2C19 activity; 59.9 ± 6.2% inhibition of CYP2C19 activity was observed.

Tabulated results:

CYP450 isoform	Substrate [µmol/L]	Metabolite	Positive control inhibitor [µmol/L]	% Inhibition	
				Negative control	Lacosamide [100 µmol/L]
CYP1A2	Phenacetin [50]	Acetaminophen	Furafylline [10]	0.0 ± 18.4	6.1 ± 6.4
CYP2A6	Coumarin [50]	7-Hydroxycoumarin	Tranylcypromine [250]	0.0 ± 4.6	-9.1 ± 8.9
	Coumarin [50]	7-Hydroxycoumarin glucuronide	Tranylcypromine [250]	0.0 ± 27.6	-23.0 ± 40.5
CYP2C9	Tolbutamide [75]	4-Hydroxy-tolbutamide	Sulfaphenazole [1]	0.0 ± 6.7	-14.1 ± 16.5
CYP2C19	S-mephenytoin [50]	4-Hydroxy-mephenytoin	Omeprazole [10]	0.0 ± 18.4	59.9 ± 6.2
CYP2D6	Dextromethorphan [8]	Dextromethorphan	Quinidine [1]	0.0 ± 2.7	-5.4 ± 5.2
CYP2E1	Chlorzoxazone [50]	6-Hydroxy-chlorzoxazone	4-Methylpyrazole [100]	0.0 ± 2.0	-1.9 ± 0.5
CYP3A4	Testosterone [50]	6ß-Hydroxy-testosterone	Ketoconazole [1]	0.0 ± 27.5	-16.9 ± 6.2

Additional information:
Data are given as mean (n = 3)
All positive control inhibitors demonstrated 100% inhibition

Study Title: Interaction of the compounds SPM 927 and SPM 12809 (Desmethyl-SPM 927) with the cytochrome P450 isoforms 1A2, 3A4, 2C9, 2C19 and 2D6.
Study №: BA 481-03 and BA 481-03-A1

The objective of this study was to evaluate potential inhibitory effects of lacosamide and its desmethylated metabolite SPM 12809 on the human hepatic cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Heterologously expressed human CYP isoforms were incubated with lacosamide and evaluated over the concentration ranges of 0.18 to 400 µmol/L and 18 to 4000 µmol/L. SPM 12809 was tested over the concentration ranges of 0.09 to 200 µmol/L and 4.6 to 10000 µmol/L. The interaction analysis of the test compounds was performed with a fully automated microtiter plate-based competitive inhibition assay with fluorescence detection.

Key Study Findings:

- The Sponsor's tabulated results are presented in the table below.
- Lacosamide, tested in the concentration range 18 to 40,000 µM, displayed inhibitory interactions with the cytochrome P450 isoforms CYP2C9, CYP2C19 and CYP3A4; K_i values were in the low mM-range.
- SPM 12809 displayed no interactions with the cytochrome P450 isoforms in the concentrations range tested.

Tabulated results:

CYP450 isoform	Substrate [µmol/L]	Specific Inhibitor [µmol/L]	Concentrations [µmol/L]							
			Controls		Phenytoin		Lacosamide		SPM 12809	
			IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i
CYP1A2	CEC [4.9]	Furafylline [0.023-50]	1.03	0.43	ND	ND	LD	LD	ND	ND
CYP2C9	MFC [73.5]	Sulfaphenazole [0.004-8]	0.31	0.20	81.3	41.8	10214	6555	LD	LD
CYP2C19	CEC [24.5]	Omeprazole [0.018-40]	3.31	1.79	46.3	25.1	1797	974	ND	ND
CYP2D6	AMMC [7.3]	Quinidine [0.0001-0.3]	0.017	0.009	ND	ND	LD	LD	ND	ND
CYP3A4	BFC [49.3]	Ketoconazole [0.0006-1.25]	0.033	0.021	150.3	96.5	2804	1800	ND	ND

Additional information:
LD = low interaction detected (calculation not reasonable), ND = no interaction detected

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Study Title: Inhibition of the cytochrome P450 isoforms 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 and SPM 12809.
Study №: 865

The potential inhibitory effects of lacosamide and its desmethylated metabolite SPM 12809 on the human hepatic cytochrome P450 enzymes CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2E1, and CYP3A5 were evaluated. Heterologously expressed human CYP isoforms were incubated with lacosamide was evaluated over the concentration range of 18 to 40000 µmol/L (4.5 µg/mL to 10 mg/mL). SPM 12809 was tested over the concentration range of 5 to 10000 µmol/L (1.2 µg/mL to 2.3 mg/mL). The interaction analysis of the test compounds was performed with a fully automated microtiter plate-based competitive inhibition assay with fluorescence detection.

Key Study Findings:

- The Sponsor's tabulated results are presented in the table below. The results indicate that both lacosamide and SPM 12809 had no inhibitory interactions with CYP2A6, CYP2B6, CYP2C8 and CYP2E1.
- Lacosamide inhibited the isoenzyme CYP1A1 with an IC_{50} value of 47.9 mmol/L (11950 µg/mL). SPM 12809 did not inhibit CYP1A1.
- Both lacosamide and SPM 12809 inhibited the isoenzyme CYP3A5 with an IC_{50} value of 3.31 and 6.20 mmol/L, respectively.

Tabulated results:

CYP450 isoform	Substrate	Metabolite	Control inhibitor [µmol/L]	Controls	IC_{50} [µmol/L] Lacosamide	SPM 12809
CYP1A1	CEC	CHC	α-Nephthoflavone [0.002-5]	0.27	47882	ND
CYP2A6	Coumarin	7-HC	TCP [0.011-25]	0.64	ND	ND
CYP2B6	EFC	HFC	TCP [0.057-125]	9.33	ND	ND
CYP2C8	DBF	Fluorescein	Quercetin [0.005-10]	1.15	ND	ND
CYP2E1	MFC	HFC	DDTC [0.046-10]	3.24	ND	ND
CYP3A5	BFC	HFC	Ketoconazole [0.002-5]	0.27	3305	6196

Additional information: ND = no inhibition detectable
BFC = 7-benzyloxy-4-(trifluoromethyl)coumarin, CEC = 3-cyano-7-ethoxycoumarin, CHC = 3-cyano-7-hydroxycoumarin, DBF = dibenzylfluorescein, DDTC = sodium diethyldithiocarbamate hydrate, EFC = 7-ethoxy-4-trifluoromethylcoumarin, 7-HC = 7-hydroxycoumarin, HFC = 7-hydroxy-4-(trifluoromethyl)coumarin, MFC = 7-methoxy-4-(trifluoromethyl)coumarin, TCP = tranylcypromine (trans-2-phenylcyclopropylamine)

- The Sponsor concluded that "...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 inhibitory concentration markedly exceeded human SPM 927 plasma levels of 14.5 µg/mL after oral administration of 600 mg twice daily (SP588). The ratio of SPM 12809 over lacosamide was less than 20% in terms of Cmax in human plasma (SP640). The calculated IC50 values were at least 57 fold higher than the human plasma concentrations." The reviewer concurs with the Sponsor.

2.6.4.6 Excretion

The excretion profile of radioactivity in urine and feces following oral and intravenous administration of [^{14}C]-lacosamide was investigated in mice, rats and dogs. Recovery of total radioactivity was examined at intervals up to 168 hours. Further the excretion pattern of [^{14}C]-lacosamide-derived radioactivity in rat milk was examined.

Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog.
Study №: 699/48

The excretion of [^{14}C]-lacosamide-derived radioactivity was determined in urine and feces in male (n=2) and female (n=2) dogs following single oral or single intravenous administrations at a dose of 10 mg/kg (5 MBq/kg). Urine sample was collected into vessels, cooled with solid carbon dioxide, at 6, 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Feces were collected at 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Radioactivity was measured using liquid scintillation counting. The tables below show the percentage of administered dose of [^{14}C]-lacosamide-derived radioactivity excreted in urine and feces following oral and intravenous administration.

Excretion of [^{14}C]-lacosamide-derived radioactivity following a single oral and single intravenous administration of [^{14}C]-lacosamide at a dose level of 10 mg/kg.

	Percent of Administered Dose							
	Oral Route				Intravenous Route			
	Males		Females		Males		Females	
Time (hr)	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces
6	52.16	NS	15.26	NS	50.83	NS	50.12	NS
24	27.21	5.609	62.64	5.135	27.24	5.083	31.57	5.174
48	1.760	1.333	2.199	2.011	2.423	1.279	1.958	1.037
72	0.465	0.104	0.639	0.082	0.662	0.097	0.744	0.173
96	0.126	0.043	0.170	0.152	0.274	0.079	0.167	0.091
120	0.089	0.040	0.139	0.066	0.137	0.043	0.172	0.035
144	0.067	0.017	0.072	0.028	0.137	0.024	0.089	0.032
168	0.052	0.015	0.092	0.054	0.053	0.014	0.033	0.052
Total	81.94	7.161	81.21	7.528	81.76	6.618	84.86	6.595

NS: No sample was collected

Key Study Findings:

- The mean recovery of radioactivity of the administered oral dose was 92.1% and 91.8% in males and females, respectively. Following intravenous administration, the mean recovery of radioactivity was 95.0% and 94.8% of the administered dose in males and females, respectively.
- Radioactivity was excreted primarily in the urine following both oral and intravenous administration. Urinary excretion accounting for approximately 82% (oral) and 82% to 85% (intravenous) of the administered dose.
- Elimination of [^{14}C]-lacosamide-derived radioactivity was rapid but prolonged; the greater proportion of the [^{14}C]-lacosamide-derived radioactivity was recovered within 24 hours after dosing; 85% to 86% (oral) and 85% to 89% (intravenous) of the dose was recovered. Radioactivity was still measurable at 168 hours after dosing.
- Fecal elimination was a minor route of excretion of [^{14}C]-lacosamide-derived radioactivity following both oral and intravenous administration.

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Radioactivity excreted in feces accounted for about 7% to 8% (oral) and 6% (intravenous) of the administered dose.

- The elimination profile of [^{14}C]-lacosamide suggest that biliary excretion appear to be a minor route of elimination.

Study Title: Bioavailability and excretion of [14C]-ADD 23407 in male beagle dogs following single administration.
Study №: F232

The excretion of [^{14}C]-lacosamide-derived radioactivity was determined in urine and feces in male (n=3) Beagle dogs following single oral or single intravenous administrations at a dose of 10 mg/kg (5 MBq/kg). Urine sample was collected at 0-4, 4-24, 24-48, and 48-72 hours interval after dosing. Feces were collected at the following time interval: 0-24, 24-48, and 48-72 hours post-dosing. Radioactivity was measured using liquid scintillation counting. Lower limit of qualification was defined as two times over background level.

Key Study Findings:

- Based on the data presented in the table below, radioactivity was mainly recovered in urine regardless of the route of administration. Excretion balance was 65.27% (mean) and 76.75% (mean) over a 0-72 hour period following intravenous and oral administration, respectively.
- Renal elimination of [^{14}C]-lacosamide was rapid; the greater proportion of the [^{14}C]-lacosamide-derived radioactivity was recovered within 24 hours with a large inter-individual variability. At 24 hours after dosing, 71.99% (oral) and 57.7% (intravenous) of the dose was recovered.
- A small percentage of [^{14}C]-lacosamide-derived radioactivity was recovered in feces following both routes of administration.

	Percent of Administered Dose							
	Intravenous Route				Oral Route			
	201M	202M	203M	Mean ± SD	201M	202M	203M	Mean
Time (hr)								
				Urine				
4				2.41 ± -				0.0 ± -
24				57.69 ± 16.54				71.99 ± 9.89
48				5.05 ± 2.00				4.32 ± 0.23
72				0.83 ± 0.45				0.44 ± 0.34
Total	52.21	82.45	61.15	65.27 ± 15.54	71.95	88.0	70.30	76.75 ± 9.78
				Fecal				
24				4.39 ± 6.93				5.51 ± 7.63
48				2.35 ± 0.37				1.63 ± 1.20
72				0.31 ± 0.28				0.04 ± 0.06
Total	3.52	3.00	14.64	7.05 ± 6.58	4.72	2.04	14.79	7.18 ± 6.72

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Study Title: [^{14}C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat.
Study №: 0699/023

The objective of this study was to characterize the route and the percent of [^{14}C]-lacosamide-derived radioactivity in urine and feces following a single oral dose and repeated dosing. Six Sprague Dawley rats (3/sex) received a single oral gavage dose of [^{14}C]-lacosamide at 10 mg/kg (4 MBeq/kg). For the repeat-dosing study, three male rats was [^{14}C]-lacosamide at 10 mg/kg. Following dosing, rats were placed in all glass metabolism cages suitable for the separate collection of urine and feces. Urine was collected at the following time intervals after the single dose administration and on day 7 from the repeat-dosing animals: 0-6, 6-24, 24-48, 48-72, 96-120, 120-144, and 144-168 hours. Fecal excreta were collected over the following time intervals after dosing: 0-24, 24-48, 48-72, 72-96, 96-120, and 120-144 and 144-168 hours. Radioactivity was measured using liquid scintillation counting.

Key Study Findings:

- Following the single dose of [^{14}C]-lacosamide, total recoveries of radioactivity ranged from 91.77% to 94.24% (mean 92.93%) and 85.85% to 92.08% (mean 90.65%) for males and females, respectively.
- Based on the data presented in the tables below, elimination of [^{14}C]-lacosamide-derived radioactivity was principally via urine following either single or repeated dosing. Fecal excretion was a minor route of elimination following a single dose or repeated dosing. Fecal excreta accounted for a mean 7.990% (males) and 4.501% (females) following a single dose of [^{14}C]-lacosamide.
- No significant differences in route of elimination were observed in males or females after a single oral dose of [^{14}C]-lacosamide. Renal excretion was the primary route of administration for both males (70.87 ± 3.414%) and females (72.78 ± 2.742%).
- Elimination is rapid. Following a single oral dose or repeated dosing of [^{14}C]-lacosamide, the majority of [^{14}C]-lacosamide-derived radioactivity in urine was recovered in the first 24 hour period after dosing. After a single oral dose, 40.79% and 34.80% radioactivity was recovered in the urine of males and females, respectively. By 48 hours, radioactivity in the urine had dropped to 1.5% and 2.4% in males and females, respectively. Following repeated dosing, 52.81% of the radioactivity was recovered in urine. Similarly the majority of radioactivity in feces was collected in the first 24 hour interval after dosing.

Excretion of [^{14}C]-lacosamide-derived radioactivity following a single administration of [^{14}C]-lacosamide at a dose level of 10 mg/kg.

	Mean Percent of Administered Dose ± SD			
	Males		Females	
Time (hr)	Urine	Feces	Urine	Feces
0-6	27.96 ± 16.23	NS	34.66 ± 7.328	NS
0-24	NS	3.045 ± 2.934	NS	3.045 ± 2.934
6-24	40.79 ± 14.17	NS	34.80 ± 4.806	NS
24-48	1.479 ± 0.363	0.856 ± 0.550	2.445 ± 1.603	0.856 ± 0.550
48-72	0.341 ± 0.138	0.250 ± 0.145	0.537 ± 0.258	0.250 ± 0.145
72-96	0.151 ± 0.090	0.160 ± 0.129	0.176 ± 0.065	0.160 ± 0.129
96-120	0.059 ± 0.007	0.099 ± 0.063	0.066 ± 0.022	0.099 ± 0.063
120-144	0.053 ± 0.015	0.060 ± 0.010	0.052 ± 0.010	0.060 ± 0.010
144-168	0.032 ± 0.005	0.032 ± 0.005	0.035 ± 0.007	0.032 ± 0.005
0-168	70.87 ± 3.414	4.501 ± 1.955	72.78 ± 2.742	4.501 ± 1.955

NS: sample not collected

Recovery of [^{14}C]-lacosamide-derived radioactivity following seven daily oral administrations of [^{14}C]-lacosamide at a dose level of 10 mg/kg.

		Percent of Administered Dose			
		401M	402M	403M	Mean ± SD
Urine	Time (hr)				
	0-6	[redacted]		[redacted]	15.23 ± 10.89
	6-24				52.81 ± 17.17
	24-48				3.168 ± 2.656
	48-72				0.291 ± 0.120
	72-96				0.116 ± 0.005
	96-120				0.061 ± 0.017
	120-144				0.044 ± 0.004
	144-168				0.085 ± 0.095
	0-168				71.81 5.519
Feces					
	0-24				6.334 ± 1.505
	24-48				1.305 ± 0.420
	48-72				0.199 ± 0.087
	72-96				0.082 ± 0.020
	96-120				0.043 ± 0.013
	120-144				0.026 ± 0.010
	144-168				0.016 ± 0.003
	0-168	[redacted]		[redacted]	8.004 ± 1.129

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Study Title: SPM 927: A study of absorption, and excretion following oral administration to the rat.
Study №: 0699/47

The objective of this study was to characterize the route and rates of excretion of [^{14}C]-lacosamide-derived radioactivity in urine and feces following oral administration of a single oral dose and repeated dosing. Six Sprague Dawley rats (3/sex) received a single

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oral gavage dose of [^{14}C]-lacosamide at 40 mg/kg (5 MBeq/kg). Following dosing, rats were placed in all glass metabolism cages suitable for the separate collection of urine and feces. Urine was collected at the following time intervals after the single dose administration: 6, 24, 48, 72, 96, 120, 120-144, and 168 hours. Fecal excreta were collected over the following time intervals after dosing: 24, 48, 72, 96, 120, 144 and 168 hours. Radioactivity was measured using liquid scintillation counting.

Key Study Findings:

- The route and rates of excretion of [^{14}C]-lacosamide-derived radioactivity were similar in male and female rats following a single oral administration of [^{14}C]-lacosamide. Recoveries of radioactivity were 94.5 ± 2.0% and 94.0 ± 0.9% for males and females, respectively.
- Renal elimination represented the principal route of elimination with means of 76.6 ± 1.5% and 82.6 ± 4.6% of the dose recovered from males and females, respectively.
- Excretion was rapid with most of the dose recovered within 24 hours. In males and females, 50.85 ± 4.016% and 43.93 ± 3.21% of the dose was recovered, respectively.
- Excretion of [^{14}C]-lacosamide-derived radioactivity was minimal. Elimination in feces was 8.0 ± 0.9% and 4.1 ± 1.2% of the administered dose in male and female rats, respectively.

Excretion of [^{14}C]-lacosamide-derived radioactivity following a single administration of [^{14}C]-lacosamide at a dose level of 40 mg/kg.

	Mean Percent of Administered Dose ± SD			
	Males		Females	
Time (hr)	Urine	Feces	Urine	Feces
6	21.44 ± 6.635	NS	34.62 ± 7.609	NS
24	50.86 ± 4.016	7.198 ± 696	43.93 ± 3.218	3.398 ± 1.233
48	3.482 ± 01.491	0.584 ± 0.220	3.168 ± 1.054	0.493 ± 0.144
72	0.484 ± 0.127	0.155 ± 0.063	0.409 ± 0.141	0.103 ± 0.015
96	0.172 ± 0.036	0.067 ± 0.012	0.201 ± 0.045	0.070 ± 0.007
120	0.091 ± 0.010	0.027 ± 0.002	0.134 ± 0.028	0.033 ± 0.010
144	0.052 ± 0.002	0.005 ± 0.010	0.083 ± 0.014	0.017 ± 0.016
168	0.048 ± 0.015	BLQ	0.056 ± 0.018	0.011 ± 0.010
Total	76.62 ± 1.499	8.037 ± 0.895	82.60 ± 4.617	4.125 ± 1.173

Study Title: <u>Absorption, distribution, metabolism, and excretion of [^{14}C]-ADD 234037 in Sprague Dawley rats following either a single intravenous or oral administration.</u>
Study №: F212

The objective of this study was to assess the excretion of [^{14}C]-lacosamide in Sprague Dawley rats following either a single intravenous or oral administration. Six Sprague Dawley rats (3/group) received either a single oral gavage or intravenous dose of [^{14}C]-

lacosamide at 10 mg/kg. Following dosing, rats were placed in a metabolism cages suitable for the separate collection of urine and feces. Urine was collected at the following time intervals after dosing: 0-4, 4-24, 24-48, and 48-72 hours. Fecal excreta were collected over the following time intervals after dosing: 0-24, 24-48, and 48-72 hours. Radioactivity was measured using liquid scintillation counting.

Key Study Findings:

- Regardless of the route of administration, excretion of [^{14}C-lacosamide] was primary in the urine. Following oral and intravenous administration, 70.56 ± 2.69% (mean) and 63.82 ± 6.48% (mean) of the total dose was recovered in the urine over the 72 hours collection period, respectively.
- Only a small percentage of the total [^{14}C]-lacosamide-derived radioactivity was recovered in feces. Total mean percent of dose of [^{14}C]-lacosamide-derived radioactivity recovered in decal excreta was 17.61 ± 6.69% and 16.26 ± 3.09%, respectively.
- Excretion was rapid with 41.46 ± 12.08% (intravenous) to 54.70 ± 11.48% (oral) of the radioactivity being recovered in urine within 24 hours.

Study Title: SPM 927: A study of absorption, distribution, metabolism and excretion following oral administration to the mouse.
Study №: 699/46

Excretion of [^{14}C]-lacosamide in urine and feces was investigated in CD-1 mice (n = 9/sex) following a single oral administration at a dose level of 20 mg/kg (5 MBq/kg). Groups of three mice per sex were placed in metabolism cages after receiving the single oral dose of [^{14}C]-lacosamide. Urine and feces were collected at 6, 24, 48, 72, 96, 120, 144 and 168 hours following dose administration. Fecal excreta were collected at 24, 48, 72, 96, 120, and 168 hours. Using liquid scintillation counting, radioactivity was determined in all samples.

Key Study Findings:

- Mean recoveries of [^{14}C]-lacosamide-derived radioactivity was 90.1 ± 4.7% (males) and 88.7 ± 3.0% (females).
- Excretion of [^{14}C]-lacosamide-derived radioactivity was rapid with > 84% (mean) of the dose recovered within 48 hours.
- Renal elimination represented the principal route of excretion with mean recoveries of 58.6% ± 17.7% (males) and 57.0% ± 14.4% (female) of the administered dose excreted via urine.
- Only a small percentage of the total [^{14}C]-lacosamide-derived radioactivity was recovered in feces. Total mean percent of dose of [^{14}C]-lacosamide-derived radioactivity recovered in fecal excreta was 4.5% ± 2.0% and 5.3% ± 2.0% for males and females, respectively.

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- Excretion was rapid with > 84% (mean) of the dose recovered within 48 hours.

Study Title: (14C)-SPM 927: Placental transfer, lacteal secretion and transfer to suckling neonates in the rat.
Study №: 699/15

The lacteal secretion of [^{14}C]-lacosamide following oral administration was investigated in suckling dams. Suckling dams received a single oral dose of 10 mg/kg [^{14}C]-lacosamide on day 10 post-partum. Samples of milk and plasma were collected at 20 minutes, 1, 2, 4, 8 and 24 hours after dosing. Liquid scintillation was used to measure [^{14}C]-lacosamide-derived radioactivity in milk and plasma.

Key Study Findings:

- Based on the Sponsor's table of results presented below, [^{14}C]-lacosamide is excreted into the milk. Concentrations of [^{14}C]-lacosamide-derived radioactivity in milk peaked at 2 hours after oral dosing (7.9 µg eq/g) and declined to 0.31 µg eq/g at 24 hours post-dosing.
- In plasma, concentrations of [^{14}C]-lacosamide-derived radioactivity peaked at 1 hour after oral dosing (8.6 µg eq/g); declining to 0.34 µg eq/g at 24 hours post-dosing.
- Mean milk over plasma ratios increased from 0.7:1 at 30 minutes to 2.5:1 at 8 hours and then decreasing to 0.9:1 at 24 hours post-dosing.

Concentrations of radioactivity in milk and plasma following a single oral administration of (^{14}C)-SPM 927 to rats on day 10 *post-partum* at a nominal dose level of 10 mg/kg body weight (group B)

Animal number and sex	Sampling time	Radioactivity concentration (µg equiv/g) Milk	Mean	Plasma	Mean	Milk/plasma ratio	Mean
170F						0.72	
171F	30 min		4.81		6.62	0.71	0.73
172F						0.75	
156F						0.86	
167F	1 h		7.05		8.55	0.86	0.83
173F						0.76	
159F						1.13	
162F	2 h		7.87		6.66	1.01	1.18
163F						1.41	
153F						1.39	
158F	4 h		7.84		5.32	1.49	1.47
168F						1.53	
152F						2.11	
157F	8 h		3.61		1.54	2.18	2.45
164F						3.05	
1F						1.04	
2F	24 h		0.31		0.34	0.84	0.89
9F						0.78	

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2.6.4.7 Pharmacokinetic drug interactions

Study Title: <u>Transport of SPM 927 across Caco-2 monloayer – Investigation of P-glycoprotein involvement</u>.
Study №: 651

The objective of the study was to investigate the permeability of lacosamide across Caco-2 cell monolayer. The involvement of active transport in the permeability of lacosamide, the apparent permeability coefficients for transport in both directions, apical tobasolateral (AB) and basolateral to apical (BA), were ascertained. In addition, the ability of lacosamide to modulate the P-glycoprotein (Pgp) mediated transport of digoxin was also investigated over a concentration range from 10 µM to 3 mM.

Key Study Findings:

- Lacosamide was not a substrate for P-glycoprotein.
- Lacosamide did not influence the transport of digoxin across the Caco-2 cell monolayer across the concentration range of 10 µM to 3 mM.
- Lacosamide was not a substrate for other active transporters. 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.

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

Lacosamide is rapidly absorbed following oral administration with an absolute oral bioavailability in the range of 77% to 94%. Lacosamide and/or its metabolite(s) are extensively distributed in tissues following oral administration and cross the blood brain barrier and placenta. The compound is weakly bound to plasma proteins in vitro; in mouse, rat, dog and human, unbound fraction of 94%, 95%, 83% and 94%, respectively. Lacosamide undergoes metabolism primarily via demethylation, hydroxylation and deacetylation. The O-demethyl metabolite SPM 12809 is the primary metabolite and is common in rats, dog and monkey. The desacetyl metabolite SPM 6912 occurs in mouse and human. In rabbit, rat and dog, hydroxylation is the favored route of metabolism of lacosamide. In vitro incubation of lacosamide with the recombinant CYP2C19 suggested that CYP2C19 is able to catalyze the metabolism of lacosamide.

Following oral and intravenous administration, lacosamide and its metabolites are rapidly excreted primarily in the urine. Mice, rats, dogs and humans displayed similar pattern of excretion of lacosamide; unchanged lacosamide and the desmethyl metabolite SPM 12809 were identified as the principal component in urine.

2.6.4.10 Tables and figures to include comparative TK summary