Type IV hypersensitivity reaction

Investigations
Alanine Aminotransferase Increased
Lipase increased
Aspartate Aminotransferase Increased
Eosinophil Count Increased
Granulocyte Count Decreased
Hepatic Enzyme Abnormal
Hepatic Enzyme Increased
Liver Function Test Abnormal
Neutrophil Count Decreased
Platelet Count Decreased
Lymphocyte count increased
White blood cell count increased
Monocyte count increased
Basophil count increased
White blood cell morphology abnormal
Biopsy liver abnormal
Biopsy kidney abnormal
Biopsy lung abnormal
Immunology test abnormal
Biopsy skin abnormal
Urinary casts

Musculoskeletal and connective tissue disorders
Arthritis
Myositis
Polyarthritis
Joint swelling
Joint warmth
Arthralgia
Arthropathy

Neoplasm, benign, malignant and unspecified
Pseudolymphoma

Renal and urinary disorders
Nephropathy toxic
Nephritis
Nephropathy toxic
Renal failure
Proteinuria
Hematuria
Oliguria
Nephrotic syndrome
Nephritis allergic
Nephritic syndrome
Nephritis interstitial
Eosinophilic cystitis[a]

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease
Pneumonitis
Alveolitis
Alveolitis allergic
Eosinophilic bronchitis[a]
Eosinophilic pneumonia[a]

Skin and subcutaneous tissue disorders
Eosinophilic cellulitis[a]

Laboratory value criteria
Eosinophils % ≥10%
Eosinophils absolute ≥0.5G/L
Neutrophils absolute <1.5G/L
Platelets ≤100G/L
ALT ≥2xULN
AST ≥2xULN

ALT=alanine aminotransferase; AST=aspartate aminotranseras; iv=intravenous; LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities; SOC=system organ class; ULN=upper limit of normal
a Preferred term is included in the MedDRA Version 11.0 SOC of 'Blood and lymphatic disorders' in the document provided by the Division. For this table, however, the preferred term is listed under the Primary SOC for MedDRA Version 9.1 (which is utilized in the original submission and this response).

Appendix 4. Adverse events suggestive of fever, rash, or lymphadenopathy (Group B) in subjects treated with LCM as submitted on (08/14/08 submission)

MedDRA® SOC/Preferred term
Blood and lymphatic system disorders
Lymphadenitis
Lymphadenopathy
Lymphadenopathy Mediastinal

General disorders and administration site conditions
Pyrexia

Immune system disorders
Drug rash with eosinophilia and systemic symptoms[a]

Skin and subcutaneous tissue disorders
Dermatitis Allergic
Rash
Rash Erythematous
Rash Generalised
Rash Macular
Rash Macular-Papular
Rash Morbilliform
Rash Papular
Rash Pruritic
Rash Psoriaform
Drug Eruption
Uriticaria
Toxic skin eruption
Exfoliative rash
Skin exfoliation
Rash vesicular

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iv=intravenous; LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities; SOC=system organ class
a Preferred term is included in the MedDRA Version 11.0 SOC of 'Skin and subcutaneous tissue disorders' in the document provided by the Division. For this table, however, the preferred term is listed under the Primary SOC for MedDRA Version 9.1 (which is utilized in the original submission and this response).

Appendix 5. Summary table of potential cases of multiorgan hypersensitivity identified in lacosamide trials, using the FDA suggested approach. Cases added in 8/08 are bolded.

Subjects with new or revised narratives based on identification of a potential case of multi-organ hypersensitivity using the Division-directed algorithm

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a]: AE or lab value criteria	AE outcome
Phase 1				
588008053	588008053	Revised	**Group A: Joint swelling**	**Ongoing**
			Group B: Rash pruritic (18 Oct 2000),	**Recovered/resolved**
			Rash pruritic (19 Oct 2000),	**Recovered/resolved**
			Rash pruritic (19 Oct 2000),	**Recovered/resolved**
			Rash pruritic (20 Oct 2000)	**Recovered/resolved**
			Rash (26 Oct 2000)	**Recovered/resolved**
640082076[b,c]	**640082076**	**Revised**	**Group A: Hypersensitivity**	**Recovered/resolved**
			Group B: Skin exfoliation	**Recovered/resolved**
641080204	**641080204**	**New**	**Group A: Arthralgia**	**Recovered/resolved**
			Group B: Lymphadenopathy	**Recovered/resolved**
641080501	641080501	New	Group A: Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Lymphadenopathy	Recovered/resolved
836000010	836000010	New	Group A: ALT increased	Resolved
			Group B: Rash	Resolved
Partial-onset seizures				
607001454	607001454	Revised	Group A: Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Rash erythematous	Not yet completely resolved
615010052	598003003	New	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Dermatitis allergic	Recovered/resolved
615011028	**667012406**	**New**	**Group A: Haematuria**	**Recovered/resolved**
			Group B: Pyrexia	**Recovered/resolved**

Appendix 5. Cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a]: AE or lab value criteria	AE outcome
667010102	667010102	Revised	Group A: Arthralgia	Recovered/resolved
			Group B: Rash (05 Mar 2003),	Recovered/resolved
			Rash (09 Apr 2003)	Recovered/resolved
667011005[c]	667011005	Revised	Group A: Hypersensitivity	Recovered/resolved
			Group B: Rash	Recovered/resolved
667011801	667011801	Revised	Group A: Eosinophil count increased,	Recovered/resolved
			Eosinophil count increased,	Recovered/resolved
			Eosinophils % ≥10%,	NA (lab value)
			Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Lymphadenopathy	Recovered/resolved
667011814	667011814	Revised	Group A: Joint swelling	Recovered/resolved
			Group B: Rash	Recovered/resolved
667013511	667013511	Revised	Group A: Eosinophils % ≥10%,	NA (lab value)
			Eosinophils absolute ≥0.5G/L,	NA (lab value)
			Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved
755100804[d]	755100804	Revised	Group A: Leukopenia	Recovered/resolved
			Group B: Rash	Recovered/resolved
755124101	755124101	Revised	Group A: Eosinophils % ≥10%,	NA (lab value)
			Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved
756012005	754012005	Revised	Group A: Neutropenia,	Recovered/resolved
			Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved

Appendix 5. Cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a]: AE or lab value criteria	AE outcome
756012201[b]	754012201	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Pyrexia,	Recovered/resolved
			White blood cell count increased	**Recovered/resolved**
756012402	754012402	Revised	**Group A: White blood cell count increased**	**Recovered/resolved**
			Group B: Pyrexia	**Recovered/resolved**
756016106	754016106	New	**Group A: Arthralgia**	**Recovered/resolved**
			Group B: Pyrexia	**Recovered/resolved**
757150001	667017720	Revised	Group A: ALT ≥2xULN	NA (lab value)
			Group B: Rash	Recovered/resolved
DNP				
614001807	614001807	Revised	Group A: ALT ≥2xULN	NA (lab value)
			Group B: Pyrexia	Recovered/resolved
665010093	614001200	Revised	**Group A: Joint swelling**	**Recovered/resolved**
			Group B: Pyrexia	**Recovered/resolved**
742012705[d]	742012705	Revised	Group A: ALT ≥2xULN,	NA (lab value)
			AST ≥2xULN,	NA (lab value)
			Hepatic enzyme increased	Not recovered/not resolved
			Group B: Pyrexia	Recovered/resolved
742016303	742016303	Revised	Group A: ALT ≥2xULN	NA (lab value)
			Group B: Rash	Not recovered/not resolved
745111802	768111802	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved

Appendix 5. Cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a]: AE or lab value criteria	AE outcome
745114718	768114718	New	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash papular	Recovered/resolved
745174208	742014208	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved
745175804	742015804	New	Group A: Eosinophils % ≥10%, Eosinophils absolute ≥0.5G/L	NA (lab value) NA (lab value)
			Group B: Pyrexia	Recovered/resolved
745176209	742016209	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash generalised	Recovered/resolved
746014104	743014104	Revised	Group A: ALT ≥2xULN, AST ≥2xULN, Eosinophils absolute ≥0.5G/L, Hepatic enzyme increased	NA (lab value) NA (lab value) NA (lab value) Not recovered/not resolved
			Group B: Rash	Recovered/resolved
768108312	768108312	Revised	Group A: AST ≥2xULN, Eosinophils absolute ≥0.5G/L, Hepatic enzyme increased	NA (lab value) NA (lab value) Recovering/resolving
			Group B: Pyrexia	Recovered/resolved
768109109	768109109	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash	Not recovered/not resolved

Appendix 5. cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a]: AE or lab value criteria	AE outcome
768109712	768109712	Revised	**Group A: Haematuria**	**Not recovered/not resolved**
			Group B: Rash (30 Mar 2005),	**Recovered/resolved**
			Rash (31 Mar 2005)	**Recovered/resolved**
768109807	768109807	Revised	**Group A: Arthralgia (18 May 2005),**	**Recovered/resolved**
			Arthralgia (20 May 2005),	**Recovered/resolved**
			Arthralgia (24 May 2005)	**Not recovered/not resolved**
			Group B: Pyrexia (18 May 2005),	**Recovered/resolved**
			Pyrexia (20 May 2005)	**Recovered/resolved**
768111003	768111003	Revised	Group A: Eosinophils % ≥10%,	NA (lab value)
			Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash (11 Aug 2005),	Recovered/resolved
			Rash (25 Aug 2005),	Recovered/resolved
			Rash (10 Sep 2005)	Recovered/resolved
768112501	768112501	Revised	Group A: Eosinophils % ≥10%,	NA (lab value)
			Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash pruritic	Recovered/resolved
830102604	830102604	Revised	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Rash	Recovered/resolved
830105613	830105613	New	Group A: ALT ≥2xULN	NA (lab value)
			Group B: Dermatitis allergic	Recovered/resolved
Neuropathic pain of mixed origin				
611001024	611001024	Revised	Group A: Hepatic enzyme increased	Recovered/resolved
			Group B: Rash pruritic	Recovered/resolved

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DNP=diabetic neuropathic pain; lab=laboratory; NA=not applicable; ULN=upper limit of normal

a Basis of identification is 'Group A+B', in which a subject was reported to experience an AE or have a lab value suggestive of internal organ involvement (Group A) and at least 1 AE suggestive of fever, rash, or lymphadenopathy (Group B) within 28 days in order for a case to be identified as potential multi-organ hypersensitivity. **b Narrative has been updated based on inclusion of additional AE preferred terms requested by the Division. c In the response to the 12 Jun 2008 request, subject was identified in the table based on selected MedDRA preferred terms of medical importance. Based on the request of the Division to add hepatitis and hypersensitivity to Group A, the subject has been moved to this table based on the Division-directed algorithm and thus no longer appears in the table based on selected MedDRA preferred terms of medical importance. d** Subject was randomized to placebo.

Note: Based on the data cut-off for the 120-day safety update, 12 Jun 2007.Source: Sponsor's table, 8/18/08 submission.

Appendix 6. Summary table of potential cases of multiorgan hypersensitivity identified in lacosamide trials, using the sponsor's important medical event approach (8/08).

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a,b]: MedDRA® Preferred Term (reported term)	AE outcome
Phase 1				
587008016	587008016	Revised	Hypersensitivity (impression of increased sensitivity)	Recovered/resolved
588008061	588008061	Revised	Hepatitis (suspect on drug induced hepatitis)	Recovered/resolved[c]
640082076	640082076	New	Hypersensitivity (hypersensitivity)	Recovered/resolved
Partial-onset seizures				
615010976	667012301	New	Hypersensitivity (09 Mar 2003) (allergies), Hypersensitivity (28 Apr 2003) (allergies)	Recovered/resolved Recovered/resolved
667011005	667011005	Revised	Hypersensitivity (allergic reaction)	Recovered/resolved
667013803	667013803	New	Hypersensitivity (allergies)	Ongoing
754013507	754013507	New	Hypersensitivity (allergies)	Recovered/resolved
756011507	754011507	Revised	Hypersensitivity (allergy symptoms)	Recovered/resolved
756012601	754012601	New	Hypersensitivity (increase allergies)	Recovered/resolved
756015005	754015005	Revised	Hypersensitivity (environmental allergies)	Not recovered/not resolved
756015608	754015608	Revised	Hypersensitivity (allergic reaction)	Recovered/resolved
DNP				
614001308	614001308	New	Hypersensitivity (exacerbation of allergies)	Recovered/resolved
614001426	314001426	Revised	Hypersensitivity (SOB secondary to allergies)	Recovered/resolved
742014104	742014104	Revised	Hypersensitivity (allergic reaction)	Recovered/resolved
745104201	768104201	Revised	Anaphylactic reaction (anaphylaxis)	Recovered/resolved
745108305	768108305	Revised	Hypersensitivity (exacerbation of allergies)	Recovered/resolved
745115009	768115009	New	Hypersensitivity (environmental allergies)	Not recovered/not resolved

Appendix 6. Cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification[a,b]: MedDRA® Preferred Term (reported term)	AE outcome
745172806	742012806	New	Hypersensitivity (intermittent environmental allergies)	Recovered/resolved
768110402	768110402	Revised	Hypersensitivity (nasal allergy)	Recovered/resolved
768113302	768113302	New	Hypersensitivity (allergic reaction/generalized swelling)	Recovered/resolved
768114108[d]	768114108	New	Hypersensitivity (worsening of environmental allergies)	Recovered/resolved
830111201	830111201	Revised	Myocarditis (toxic damage of myocard)	Fatal
830111810	830111810	New	Hypersensitivity (allergic reaction)	Recovered/resolved

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotranserase; DNP=diabetic neuropathic pain; lab=laboratory; NA=not applicable; ULN=upper limit of normal
a Basis of identification is 'Medical importance', which is an AE of hypersensitivity, anaphylactic reaction, hepatitis, or myocarditis any time after Baseline (start of trial medication).
b Subjects meeting the criteria because of a medically important event may have also had an AE or lab value within Group A or Group B; however, as this was not the basis of identification, it is not identified in the table. Information regarding additional AEs or lab values is provided in the narrative.
c The outcome of this AE is given as "not yet completely resolved" in the SP588 clinical trial report. The outcome is reported as "recovered" in this table because more information about this case has become available outside the database showing that the AE was resolved.
d Subject was randomized to placebo
Note: Includes all Phase 1 LCM trials, all oral and intravenous (iv) Phase 2 and 3 lacosamide trials in subjects with partial-onset seizures, and all oral Phase 2 and 3 LCM trials in subjects with neuropathic pain (ie, DNP, post-herpetic neuralgia, and neuropathic pain of mixed origin).
Note: Based on the data cut-off for the 120-day safety update, 12 Jun 2007.
Source: Sponsor's table, 7/16/08 submission.

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

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/s/

Maria Villalba
9/26/2008 03:59:53 PM
MEDICAL OFFICER

Sally Yasuda
9/29/2008 12:35:46 PM
INTERDISCIPLINARY

b(4)

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA:	22-253, 22-254 —
Drug:	Lacosamide (VIMPAT)
Route:	Oral (tablets — IV b(4)
Indication:	Partial Onset Seizures
Sponsor:	Schwartz Biosciences
Review Date:	7/7/08
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Neurology Drug Products, HFD-120

1. Background

Lacosamide has been proposed as adjunctive therapy of partial onset seizures in patients ≥ 16 y.o. The Sponsor has also proposed lacosamide for management of neuropathic pain associated with diabetic peripheral neuropathy in NDA —, that indication is being reviewed by HFD-170. The mechanism of action of lacosamide in either indication has not been fully characterized; it enhances slow inactivation of voltage-gated sodium channels. b(4)

The Sponsor has proposed the use of lacosamide (LCM) for partial onset seizures given orally in doses up to — mg/day, beginning with initial doses of 100 mg/day given as twice daily dosing. Intravenous LCM infusion was evaluated for temporary replacement of the oral dose in patients who are unable to take oral products. The Sponsor's recommendation for switching from oral LCM is that the initial total daily intravenous dosage should be equivalent to the total daily dosage and frequency of the oral formulation, and that it should be infused over a period of at least — minutes. b(4)

This memorandum primarily summarizes the primary safety concerns from the safety team's review of the lacosamide NDAs (22-253, 22-254 —) for adjunctive therapy for partial onset seizures. Dr. Villalba conducted the primary safety review for HFD-120. In addition to evaluating the safety database in the epilepsy population, Dr. Villalba has also summarized the results of a consult from Dr. Stephen Grant of the Division of Cardiovascular and Renal Products (DCRP) regarding PR prolongation and cardiac safety, as well as the pertinent safety results from the diabetic peripheral neuropathy (DPN) submission in NDA — that was formally reviewed by Dr. Prokovnichka from the Division of Anesthesia, Analgesia and Rheumatologic Products (DAARP). Please refer to Dr. Villalba's review for detailed safety considerations. b(4)

2. Summary of Findings from the Safety Review

2.1 Sources of Data

The clinical data are from studies submitted as part of the NDAs. Dr. Villalba's review covered safety for NDA 22-253 (tablets), 22-254 (IV infusion) —. She b(4)

has focused on safety in the phase 2/3 epilepsy studies (oral tablet and IV). The Phase 2/3 epilepsy studies with the oral tablet are referred to as EP S1 (three placebo controlled studies) and EP S2 (includes EPS1 and open label studies). Dr. Villalba has also reviewed safety in phase 1 studies and in the phase 2/3 studies with the oral capsule that were not included in the ISS safety pool. In addition, Dr. Villalba discusses pertinent safety findings in the DPN population, as identified in the DAARP review. For details regarding exposure in the safety pool, please refer to Dr. Villalba's review.

2.3 Significant Safety Findings

2.3.1 Deaths

Dr. Villalba notes that there were 9 deaths, all in patients taking LCM, across 1327 subjects in the Phase 2/3 LCM partial onset seizure population. One of these occurred in the LCM-treated group in EP S1 (1/944=0.1%). There were no deaths in the Phase 1 studies, Phase 2/3 trials with IV infusion, or oral capsule studies. Of the 9 deaths, 4 were considered possible sudden unexpected death in epilepsy (SUDEP) and 1 was a completed suicide. Suicidality will be discussed later in the review. The other 4 deaths included 1 road traffic accident, 1 due to intracranial hypertension, 1 glioblastoma, and 1 cerebral hemorrhage thought secondary to injury during an epileptic seizure. Dr. Villalba believes that there is not a pattern suggesting that the 9 deaths were drug-related. I agree.

In EP Pool S2, the estimated rate of SUDEP is 0.002 per patient year. As Dr. Villalba has discussed, the rate of SUDEP in the present LCM application is in the range expected in this population, based on that described in the LAMICTAL label (0.0005 for the general population of patients with epilepsy to 0.005 for patients with refractory epilepsy in patients not receiving LAMICTAL).

In addition to the deaths in the epilepsy population, there were 15 deaths across 1566 subjects in the Phase 2/3 LCM DPN population. No deaths occurred on placebo (0/291). Four were in the controlled studies (4/1023). Eight were cardiac-related (3 were in the placebo controlled studies), 1 was a completed suicide (72 days after last dose of LCM), 1 was the result of head trauma/subdural hematoma/cardiopulmonary failure, and 5 were cancer-related (ovarian, pancreatic, bronchial, colon, and leukemia). The cardiac deaths (ventricular fibrillation, myocardial infarction, heart failure (n=2), myocarditis, cardiac arrest (n=2), and sudden death) occurred in patients with previous cardiovascular history, including diabetes plus hypertension, coronary artery disease, cerebrovascular disease, or peripheral vascular disease. In two of the cases of cardiac death (ventricular fibrillation and cardiac arrest), Dr. Prokovnichka did not believe that the relationship to LCM could be ruled out given the limited information provided.

An additional death was reported in the DPN population. This death was due to myocarditis/toxic hepatitis and occurred 2 ½ months following the last time LCM was dispensed for this patient, and the last date of administration was unknown. According to the sponsor at a teleconference on 6/12/08, a 3-month supply had been dispensed. The patient had taken LCM for more than 1 year. The toxic hepatitis was said to be alcoholic, although it is stated that the subject did not have a history of alcohol abuse. There is no

further information available in the submission and the sponsor is not able to provide more details. We are concerned that this case could be consistent with a multi-organ hypersensitivity reaction.

2.3.2 Other Serious Adverse Events

Overview of EP S1 and S2 - Dr. Villalba notes that in placebo-controlled trials (EP Pool S1), the rate of treatment emergent (TE) serious adverse events (SAE) was 6.5% in LCM-treated subjects compared to 3.8% in subjects on placebo. Dr. Villalba does not find a clear dose-response for SAEs among LCM-treated patients. The most frequently reported TE SAEs in the epilepsy population were in the Nervous System disorders System Organ Class (SOC) (2.1% for LCM and 1.6% for placebo), with the most frequent preferred term (PT) being convulsion for both LCM and placebo-treated patients (0.8% for placebo and 0.8% across LCM doses). The next most frequent TE SAEs were in the Psychiatric disorders SOC (0.7% for LCM and 0 for placebo-treated patients). The psychiatric disorders included 1 case of hallucinations and 3 cases of psychosis. There was 1 case each of suicide, and suicide attempt. The most frequent PTs in EP Pool S2 were convulsions (7.9%) and dizziness (2.9%). As Dr. Villalba notes determination of causality is difficult.

DPN Database - Dr. Villalba notes that in the DPN database, the highest proportions of SAEs were in the cardiac disorders SOC (angina, coronary artery disease, A-fib, a-flutter, and bradycardia) and the Nervous system disorder SOC (loss of consciousness and transient ischemic attack). SAEs in the DPN population were higher in the LCM treated patients (7.5%) compared to placebo (5.2%). The frequency of the cardiac SAEs was similar between LCM and placebo treated patients, although most of the cardiac conduction/rhythm abnormalities recorded as SAEs were reported from subjects treated with LCM. Other significant AEs that were observed to occur more frequently in patient receiving LCM vs placebo were syncope related events (7.3% vs 2.4%, respectively).

Bradycardia - In the Phase 2/3 infusion studies there was 1 SAE of bradycardia reported. Dr. Villalba describes this case in detail in her review, and I will summarize it here. This was a 48 y.o. white male with a prior history of hypertension who was also taking the ACE inhibitor perindopril, the beta-blocker acebutolol, and carbamazepine. After completing the 12-week treatment phase with oral LCM 200 mg/day he was rolled over into the open label extension. He had been in the OLP for approximately 6 months and had been taking oral LCM 300 mg/day for 74 days prior to enrolling in the IV trial. The AE occurred 7 minutes into the 3rd infusion of LCM 150 mg given over 15 minutes. Heart rate (HR) pre-dose was 62 bpm with a BP of 120/80; HR dropped to 26 bpm with a blood pressure of 100/60 mm Hg and there was no prolongation of PR or QRS. The LCM infusion was stopped due to the AE and the ECG changes were reported to be resolved 4 minutes after onset. Dr. Villalba notes that the plasma concentrations of LCM in this subject were less than 9 µg/ml after the first 2 doses and after the infusion was stopped.

Two of the Sponsor's cardiologists evaluated the case and diagnosed it as either bradycardia with junctional escape, or AV block with sinus exit block. Dr. Stephen Grant, the FDA cardiologist who evaluated this case, believes it is likely a vasovagal reaction. Dr. Villalba believes that a relationship between the infusion of the drug and the profound bradycardia is biologically plausible. She refers to the time course of the event, as well as the known PR and QRS prolongation observed in nonclinical studies in dogs at doses equivalent to 300 mg bid in humans (and with plasma concentrations of approximately 14.5 µg/ml). Dr. Villalba notes that taking a beta blocker may have predisposed this subject to the LCM effects on the heart rate. I agree with her assessment.

Hepatitis/Nephritis/Multi-Organ Hypersensitivity - Dr. Villalba describes in detail a case of symptomatic hepatitis/nephritis occurring 12 days after the final dose of lacosamide in a healthy volunteer. Increased liver enzymes (AST/GOT >30X ULN; ALT/GPT >10X ULN) along with proteinuria and casts (unknown values) were reported. No bilirubin was measured at the time of this AE. Transaminases were returning to normal approximately 1 week later. There is a discrepancy regarding the bilirubin levels at the time that the transaminases were returning to normal, with levels of 22 mg/dl reported in the ISS but 22 µmol/l (1.3 mg/dl) reported to the FDA in a later communication. Because there is no confirmed bilirubin value at the time of the AE, a Hy's law case cannot be ruled out. Approximately 1 month after the patient became symptomatic, laboratory values normal. Viral causes for hepatitis were ruled out. A gastroenterologist diagnosed acute drug-induced hepatitis without any sequelae. A dermatologist interpreted this event as a possible delayed allergic reaction toward the trial medication. Dr. Villalba believes that drug induced hepatitis, or even a multi-organ hypersensitivity syndrome, cannot be ruled out, and notes that the fact that the drug was stopped because of study completion may have prevented the patient for having more severe/irreversible hepatic damage. I agree.

2.3.3 Dropouts and Other Significant Adverse Events

Overall, 17.1% in the LCM group in EP S1 had treatment emergent AE that led to drop out compared to 4.9% on placebo. Across the placebo controlled trials in EPS1, there was a dose-dependent increase in premature discontinuations based on SOC. The majority of discontinuations due to AEs occurred during the titration period. The most common PTs leading to discontinuation were dizziness, ataxia, convulsion, and tremor; the overall rate for convulsion was similar for LCM and placebo. Other AEs that led to dropout were nausea, vomiting, diplopia, blurred vision and fatigue, and these showed a dose-response. The overall rate of dropouts in EPS2 was similar to EPS1. Similar events led to drop out in the DPN database. Syncope led to dropout in both the EP and DPN populations and will be discussed later.

2.3.4 Common Adverse Events

Among the most common adverse events in EPS1 were dizziness, ataxia, nystagmus, and balance disorder that are also associated with other antiepileptic drugs. Common adverse events in the DPN population were similar to the epilepsy population.

2.3.5 Laboratory findings

Evaluation of routine chemistry, hematology laboratory measurements and urinalyses did not reveal major issues of clinical concern in patients with partial-onset seizures, other than the previously identified case of hepatitis and increases in transaminases and GGT that will be discussed in section 2.3.6 of this memo.

In EPS1 neutropenia occurred in 1.3% of the total LCM group and 1.1% for placebo. There were 3 cases of treatment emergent neutropenia with granulocyte count < 1500/L that all occurred in the IV LCM group in SP616 and no cases on placebo or after oral administration in Study SP616 (7.8% in the IV infusion group vs 0% in the oral LCM group). SP616 was a phase 2/3 infusion study that was an extension to an open label study with the oral tablet. Pre-infusion neutrophil counts were available for 2 of the 3 patients; one had a neutrophil count of 2.3 and the other had a neutrophil count of 1.7 prior to the infusion. In the phase 2/3 study SP757, the rate of neutropenia was similar to that in EPS1 (1.3%). According to Dr. Villalba's review, several patients had baseline neutropenia in both SP616 and SP757, and that it was unknown whether it was acquired during EPS2 or prior to lacosamide. The clinical significance of these observations is unclear.

2.3.6 Adverse Events of Interest

Based on non-clinical and clinical trial data, and safety considerations related to other AEDs, evaluation was performed for AEs related to cardiac and ECG abnormalities, syncope, abnormal liver function, rash, seizure, memory impairment, suicidality, and weight change.

Cardiac AEs

Consistent with conduction effects identified in the nonclinical program, LCM has a dose-related effect on the cardiac conduction system. In the thorough QT (TQT) study a dose-related increase in PR interval was observed. The maximum mean changes in PR interval on Day 6 (steady-state) were observed at 1 hour post-dose and were 6.3ms, 13.6ms, and 18.2ms in the placebo, LCM 400, and LCM 800 groups, respectively. (No subject in any treatment group in the TQT study had QRS > 120 msec during the treatment phase). No evidence of orthostatic hypotension was observed. Evaluation of vital signs at protocol-specified time points in the clinical trials and in the TQT study suggests little or no effect on SBP, DBP, or heart rate with the proposed therapeutic doses of LCM oral tablet in the epilepsy population. Orthostatic changes were not measured in phase 2/3 studies.

The TQT study demonstrated a shortening of the QTc. At Tmax on day 6, the mean change in QTcI from baseline for LCM 400 mg/day compared to placebo was -9.4 msec with an upper one-sided 95% CI of -4.2; for 800 mg/day the values were -7.4 and -3.3 msec, respectively. According to the IRT review of the TQT study, adequate data upon which to base a recommendation regarding labeling for products that shorten the QT interval do not currently exist.

As Dr. Villalba has reviewed, the percentage of patients with any potentially cardiac-related AEs is 5.0% for LCM and 2.3% for placebo in EP Pool S1. The difference is driven by a higher rate of rhythm and conduction disorders, mainly PR and QRS prolongation in the LCM group. There were 4 cases of first degree AV block in the LCM group (0.4%) vs 0% on placebo.[1] Three subjects taking LCM presented conduction disorders that led to dropout (2 cases of bradycardia and 1 PR prolongation in a patient with sick sinus syndrome) in EPS1. There were no cases of second degree AV block or serious arrhythmias in EPS1 or EPS2. In the DPN database, there was 1 case of second degree AV block in a patient with prolonged PR at baseline taking LCM 400 mg daily during the DPN open label studies, and an additional patient who had second degree AV block during telemetry monitoring after a syncopal episode during LCM titration with a dose of 600 mg. No QRS prolongation was observed in the DPN controlled database. In the placebo controlled studies in DPN there were 5 AEs of first degree AV block, 4 of atrial fibrillation, 3 of atrial flutter, and 1 nodal rhythm, all in the LCM treatment group. No such cases were observed in the placebo group.

Of note, a case of 1st degree AV block occurred in a healthy volunteer when LCM was added to digoxin in a drug interaction study.

Syncope

Dr. Villalba has reviewed cases of syncope in the epilepsy population and summarized the discussion of syncope in the DPN population. Overall the rate of syncope in the controlled phase of the epilepsy and neuropathic pain studies was 0.8% for patients randomized to LCM (15/2004) and none of the patients randomized to placebo (although one patient was on placebo at the time of the event). Three cases were in the controlled phase of the epilepsy studies (2 on LCM and 1 on placebo). The overall rate of syncope/loss of consciousness in the LCM program was 1.1%. In one of the DPN cases, the patient had 2nd degree AV block identified with telemetry monitoring. Two cases had documented orthostatic hypotension on the same day of the event. Four additional cases were reported during Phase 1 studies with the oral formulation. One was unlikely drug related and 3 were consistent with vasovagal reactions. In most cases ECGs were not done at the time of the event. Based on the known effects of LCM in cardiac conduction, Dr. Villalba believes that an LCM-related cardiac cause for syncope cannot be ruled out. I agree. In addition, Dr. Villalba suggests that if future clinical studies are performed, orthostatic changes in blood pressure should be measured, especially in patients who experience syncope or pre-syncope. In addition, she recommends that Holter monitoring should be considered in clinical trial patients who experience syncope if the drug is not to be discontinued. I agree with her recommendations for such monitoring in future studies with LCM in order to further characterize the mechanism for syncope and potentially identify a strategy to minimize this risk.

[1] This number was incorrect on page 75 of Dr. Villalba's review. The summary on p. 75 of her review should state that there were 4 cases of first degree AV block in the LCM group (4/944=0.42%) vs 0% on placebo.

Division of Cardio-Renal Products (DCRP) Consultation
As suggested by the DCRP review, the increase in PR may result in clinically significant AV block and is particularly important in patients with pre-existing AV nodal disease and/or who are co-administered agents that block the AV node. DCRP recommends obtaining an ECG after LCM is titrated to steady state in such patients. I agree and suggest that in such patients a baseline ECG prior to administration should also be performed. Myocardial ischemia may potentiate the effect of LCM on the PR interval. DCRP believes that patients with diabetes and/or cardiovascular disease may be at increase risk of atrial fibrillation and/or atrial flutter following treatment with LCM. These recommendations can be addressed in labeling and should be included in considering a REMS.

Abnormal Liver Function
Dr. Villalba's review of hepatobiliary investigations and hepatobiliary disorders in the epilepsy studies suggest that LCM at doses of 200-600 mg/day may induce transaminase (ALT and AST) and GGT elevation as compared to placebo (2.4% for LCM, 1.1% for placebo). In EP S1 ALT/AST >3X ULN occurred in 0.7% on LCM vs 0% on placebo, and was not associated with abnormal bilirubin. The elevations were reversible on withdrawal of LCM (although in 1 case the patient was lost to follow-up). No cases of liver failure were observed in either the epilepsy database or in the diabetic neuropathic pain population. In addition to the transaminase elevations discussed here, one subject in a Phase 1 study had hepatitis/nephritis with elevated transaminases 10-30X ULN (with no determination of bilirubin at the time of the elevated transaminases) in a case consistent with hypersensitivity, as discussed in section 2.3.2 of this review.

Dr. Villalba recommends that liver toxicity can be addressed with [redacted] routine pharmacovigilance. [redacted] I agree with her recommendation [redacted] I also recommend that the Sponsor should include bilirubin and prothrombin time in cases of transaminase elevations in future clinical studies. Finally, in the absence of a bilirubin level, a Hy's law case cannot be rule out in the case of the subject with hepatitis/nephritis. Therefore, I suggest that [redacted] b(5)

Rash
The rate of rash in EP S1 was similar among patients treated with LCM vs placebo (3.3% in LCM vs 4.7% in placebo), with no evidence of dose response. Pruritus was more common in the LCM treatment group than in placebo, but there was no dose response observed. The rate of rash in the long-term exposure database was 6.7%. There were no cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome or toxic Epidermal Necrolysis. There were two potential cases of multi-organ hypersensitivity as previously discussed, one in the epilepsy database and one in the DPN database. In a teleconference on 6/12/08 the Sponsor was asked to further evaluate the database with respect to signals for hypersensitivity. I agree with Dr. Villalba that this hypersensitivity should be included in the WARNING and PRECAUTIONS section of the label. I also recommend that [redacted] b(5)

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Seizures
Dr. Villalba's analyses do not suggest that LCM is associated with increased risk of seizures in patients with epilepsy.

Memory Impairment
Dr. Villalba's review suggests that LCM is associated with some mental impairment (amnesia, cognitive disorder, disturbance in attention, memory impairment) as compared to placebo, with some evidence of a dose-response. Memory impairment was the most common PT in S1 and in S2.

Psychotic disorders and Psychiatric disorders
Dr. Villalba's review identified 3 patients in EP S1 who developed psychotic disorders while on LCM 300-400 mg as compared to none on placebo or in patients taking LCM 600 mg and she states that the numbers are too small to draw definitive conclusions.

Dr. Villalba also reports evidence of an effect of LCM on the mood of patients taking LCM as compared to placebo. Depression was the most frequent PT under the HLGT of Depressed mood disorders and disturbances (2.6% on LCM vs 0.5% on placebo), and there were other PT terms related to mood (depressed mood) and other mood disorders such as moodiness that also occurred more frequently in LCM than in placebo. Dr. Villalba notes that the Sponsor has not identified depression as an adverse event associated with LCM and recommends that depression should be prominent in the LCM labeling. I agree.

Suicidality
Dr. Villalba has identified a rate of suicidality-related events in the partial-onset seizure population as 0.5% (5/944) in patients taking LCM and 0.1% (1/781) in placebo patients. These rates are similar to what has been seen overall with AEDs as a class as reported in the January 2008 FDA alert (0.43% for AEDs in the epilepsy population vs 0.22% on placebo). No suicidality cases were identified in populations other than the epilepsy population. (There was 1 suicide in the DPN population that occurred 72 days after the last dose of LCM). Dr. Villalba recommends that lacosamide should carry the proposed class labeling WARNING for AEDs for the risk of suicidality. I agree.

2.3.7 Intravenous Infusion
Dr. Villalba has described the adverse events reported following IV infusion. Adverse events of interest were cardiovascular including first degree AV block (n=2), RBBB, QTc prolongation (n=2), and profound bradycardia with a question of sinus bradycardia vs AV block with sinus exit block (the latter was discussed above under serious adverse events). Of subjects with normal ECG at baseline, 1.8% developed AE of rhythm or conduction disorders with the LCM IV formulation and 1.1% discontinued the studies because of

these events. Dr. Villalba has expressed concern regarding the rate of the IV infusion as well as the population to whom it will be given. I will discuss these concerns and provide additional considerations regarding drug exposure with respect to plasma concentrations.

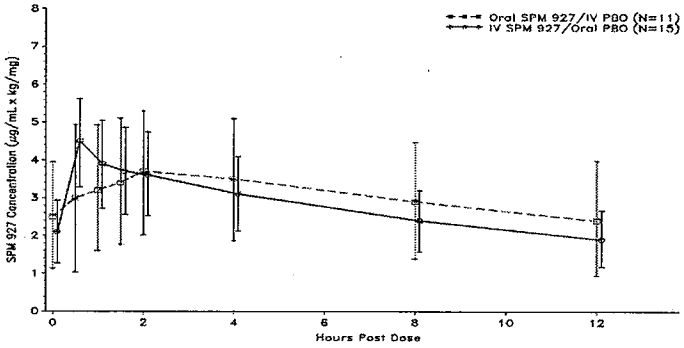
As reviewed by the Office of Clinical Pharmacology (OCP) bioequivalence (BE) was demonstrated for LCM 200 mg given IV over 30 or 60 minutes vs 200 mg given orally as a single dose (Study SP658). However, BE was not demonstrated for a 200 mg infusion given over 15 minutes compared to a 200 mg oral dose, with a mean Cmax that was approximately 24% higher after the infusion (Study SP645). Median Tmax in these studies was 0.25 hours (range 0.25-2.0) for the 15 minute infusion, 0.5 hours for the 30 minute infusion (range 0.5-2.0), and 0.75 hours for the oral dose. However, in the Phase 1 studies with oral LCM, median Tmax was generally 1-1.5 h (range 0.5-4.0)

Study SP757 was an open label trial to investigate safety and tolerability of IV LCM as a replacement of oral LCM in subjects with partial seizures who were receiving oral LCM in an open label extension trial. Subjects received IV LCM infused over 10 minutes (n=20), 15 minutes (n=100), or 30 minutes (n=40) twice daily, for 2-5 days. The daily IV LCM dose was the same as the subject's current daily dose of oral LCM. Thus, although 100 patients were exposed to the 15 minute infusion, at any given dose in the 15 minute infusion group, less than 30 patients were exposed. For example, 26 patients received the 400 mg daily dose given twice daily over 15 minutes. Following a 400 mg/day dose given twice daily over 30 minutes, mean Cmax was approximately 9.5 µg/ml (CV approximately 25%) and the maximum Cmax 13.4 µg/ml. Following a 400 mg dose given twice daily over 15 minutes, mean Cmax was approximately 10 µg/ml (CV approximately 24%) and the maximum Cmax was approximately 18 µg/ml. Although mean Cmax may only be approximately 20% higher after an IV infusion than after oral administration, some patients may have a C_{max} that is almost 2x the mean, and the rate at which the Cmax is achieved is much faster than following oral administration. Of note, the geometric mean Cmax was approximately 21 µg/ml (CV 20%) at steady state following 800 mg/day oral LCM in the TQT study. Therefore, concentrations that could be achieved following IV administration of 400 mg/day twice daily over 15 minutes approach the exposures at which an almost 20 msec PR prolongation was observed in the TQT study.

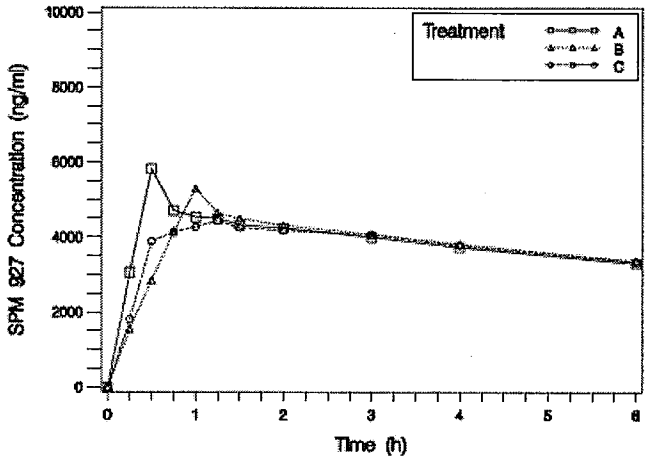
Dr. Villalba points out that the patients exposed to IV LCM in the phase 2/3 clinical studies were those who had tolerated LCM well for several months prior to being exposed to the IV formulation. Therefore, Dr. Villalba suggests that IV LCM not be approved in LCM-naïve patients. The BE study showed BE of infusion over 30 minutes compared to the oral dose, and therefore the IV formulation should not behave differently in naïve patients compared to oral administration. One concern may be tolerability due to rate of rise of the plasma concentrations after IV infusion compared to oral administration. The following figures, taken from Dr. Tandon's OCP review, can be used to consider differences in the rate of rise. The figure below is from study SP616 in patients who had been maintained on a stable dose of oral LCM and were switched to IV LCM. It can be seen that the mean rate of rise for plasma concentration after IV administration is approximately twice as fast as after oral administration, although there

is substantial variability and overlap of plasma concentrations at all time points, However, in the second figure taken from BE study (where Treatment A is 200 mg 200mg LCM 30 min infusion, Treatment B is 200 mg LCM 60 minute infusion, and Treatment C is 200 mg given orally), the mean values do not suggest a difference in the rate of rise

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



Mean plasma concentration-time curves of lacosamide for Treatments A (N=24), B (N=25), and C (N=23) – 0-6 hours



Based on these figures, it is difficult to make any conclusions about the rate of rise of plasma concentrations after IV infusion. I recommend that the IV infusion be given over 30 minutes to minimize the potential for adverse cardiac events and that the titration schedule for the intravenous formulation be the same as the titration schedule recommended for oral dosing to minimize intolerability. In addition, Dr. Villalba's recommendations regarding monitoring of ECG at steady state in patients at risk for

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adverse cardiac events should be applied to patients receiving either the IV infusion or oral administration. Finally, I recommend [redacted] b(5)

2.3.8 Adequacy of patient exposure and safety assessments

The Sponsor proposes to use LCM oral and IV formulations in patients age 16 years and older. Dr. Villalba points out that only 7 patients who were 16 or 17 years old received LCM in these studies and no patient younger than 18 was exposed to the IV formulation. There is unlikely to be a pharmacokinetic difference in patients who are 17 y.o. compared to young adults 18 y.o. and older that would result in a difference in exposure. Therefore it seems reasonable to have an indication in patients greater than 16 y.o. However, because there is little experience in patients < 17 y.o. it would be prudent to conduct studies in the pediatric age group prior to use in this group, consistent with the age range generally evaluated in pediatric studies.

Dr. Villalba has also summarized concomitant diseases and concomitant medications, with respect to cardiovascular disease, since PR prolongation and syncope have been identified as AEs of concern. Cardiac disorders at baseline were present in only 2.4% of patients in the LCM group and 4.7% of patients in the placebo group. Beta-blockers and calcium channel blockers were taken by 3.5% and 1.4%, respectively, in patients in the LCM groups. "Cardiac therapy" was taken by 0.7% in the LCM treatment group. Therefore, overall a small percentage of patients with cardiac disorders and taking cardiac and antihypertensive medications were included in the epilepsy population. I agree with Dr. Villalba's position that this lack of experience may be of concern when LCM is taken in a population of epilepsy patients that is less healthy than the population included in the clinical studies. [redacted] b(5)

Dr. Villalba recommends that there is insufficient data to support the use of the IV formulation in subjects older than 65 y.o., in naïve patients, and in patients with prevalent concomitant disease (e.g. ischemic heart disease). Dr. Villalba describes the eligibility criteria that excluded patients with heart conditions and taking certain concomitant medications that could increase or confound the potential cardiovascular toxicity of LCM. [2] Additionally, antipsychotics, anxiolytics, MAO inhibitors and antihistamines were excluded. Dr. Villalba recommends that the labeling needs to address the lack of

[2] According to Dr. Villalba's review, patients included in the epilepsy studies were relatively young (only 16 in the entire database were older than 65 years) and healthy, with no previous history of arrhythmias, prolonged QTc (>450 in male or > 470 in women), no history of 2nd degree AV block, congestive heart failure or recent history of myocardial infarction. According to Dr. Pokrovnichka's review DPN studies SP742 and 743 and 768 excluded patients with myocardial infarction or clinically relevant cardiac dysfunction within the previous 12 months or any cardiac disorder that, in the opinion of the investigator, would put the subject at risk of clinically relevant arrhythmia and/or myocardial infarction; 2° or 3 ° AV block or sinus bradycardia or tachycardia; prolonged QTc , and the randomized withdrawal substudy of Study 746 excluded patients with clinically relevant ECG abnormalities, development of sick sinus synde4rome and no pacemaker availability, myocardial infarction during the trial,New York Heart Association Class III or IV heart failure, atrial fibrillation/flutter, ventricular tachyarrhythmia, symptomatic heart block or Brugada syndrome.

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experience with these patients and should carry a WARNING regarding the unknown risks in these populations. With respect to administration of IV LCM in LCM-naïve patients, if LCM is to be infused over 30 minutes, given that the 30 minute infusion is BE to oral administration, and given that the rate of rise of plasma concentration in IV vs oral seems to be generally comparable when given over 30 minutes, I think that it could also be given to LCM-naïve patients with the titration schedule that has been recommended for oral administration. I believe that in elderly patients and patients with concomitant disease of concern, that adequate labeling could address the lack of experience and the risk factors of concern, as Dr. Villalba has recommended for other patients that have been excluded from the epilepsy studies.

2.3.9 Summary of Significant Safety Concerns:
Significant safety concerns are summarized as follows:

- SUDEP – The rate of SUDEP in this program is within the rate reported in patients with severe epilepsy. However, there were also 15 deaths in the neuropathic pain program, 8 of which were cardiac related and in patient taking LCM (3 of those were during the placebo-controlled phase).
- The most common cardiac effects were prolongation in PR and QRS. PR prolongation was identified in all populations studied. In most cases it was asymptomatic and there were no cases of second degree AV block or serious arrhythmias in the epilepsy or phase 1 studies. There were 2 cases of bradycardia with junctional escape, one in a phase 1 study with the oral tablet and one in a phase 2/3 study with the IV formulation. AV block is anticipated to occur in patients with underlying CV disease, conduction abnormalities, and patients taking other medications that prolong the PR interval. Syncope was associated with LCM, although the mechanism was unclear and ECGs were generally not available from the time of the event. In the controlled neuropathic pain population 13 cases of syncope were observed in patients treated with LCM (1.2%) as compared to none on placebo and seven cases of atrial fibrillation/flutter were observed in LCM treated patients vs none on placebo. The potential for serious adverse cardiac events was not well characterized in patients who may be predisposed to these events. These concerns should be addressed in labeling and in REMS including a Medguide. The Sponsor has proposed
- Two potential cases of drug-induced hepatitis/ multi-organ hypersensitivity have been identified. A Hy's law case cannot be ruled out. The Sponsor has been asked to further evaluate the database for hypersensitivity. Dr. Villalba recommends that the label should carry a WARNING for potential hypersensitivity reactions and that hypersensitivity be included in a REMS. I agree. In addition, I recommend

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- LCM was associated with depression and suicidality. The rate of suicidality was similar to that described for other AEDs. The label should carry a WARNING for

the risk of suicidality. Depression and suicidality should be addressed in labeling and in REMS.

- Due to the potential for increased exposure following IV administration over 15 minutes compared to that observed following oral administration, I recommend that the maximum rate of infusion for the IV formulation should not be less than 30 minutes. If it is to be infused over 30 minutes, given that the 30 minute infusion is BE to oral administration, and given that the rate of rise of plasma concentration in IV vs oral seems to be generally comparable when given over 30 minutes, I think that it could also be given to LCM-naïve patients with the titration schedule that has been recommended for oral administration. The concerns regarding administration in patients at risk for serious cardiac events would apply in these patients (or any patient given IV LCM), just as they do in patient given LCM orally.
- Although not discussed above, the Sponsor has proposed including pregnancy registry contact information for both the NAAED as well as the Sponsor's own registry. I have discussed this with Dr. Alice Hughes who has also received input from Karen Feibus from the Maternal Health Team. Due to concern regarding possible confusion and failure to participate in any registry, I recommend

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2.3.10 Postmarketing Risk management Plan

Dr. Villalba recommends that this drug should have a REMS beyond labeling and routine surveillance for the effects on cardiac conduction, syncope, potential multi-organ hypersensitivity reactions, and the risk of suicidality. I agree with this recommendation.

2.3.11 Conclusions

Dr. Villalba concludes that lacosamide is safe at doses of 200 to 400 mg daily, and that doses of 600 mg daily are associated with increased toxicity. Dr. Villalba recommends that the maximum recommended dose should be 400 mg daily. I agree with her recommendation. In addition, the labeling should recommend a maximum rate of infusion for the IV formulation that should not be less than 30 minutes. Dr. Villalba suggests that the IV formulation should be used as temporary replacement of the oral formulation in patients who are at a stable dose of oral LCM. However, if it is to be infused over 30 minutes, given that the 30 minute infusion is BE to oral administration, and given that the rate of rise in plasma concentrations of LCM when given IV vs oral seems to be generally comparable when given over 30 minutes, I think that it could also be given to LCM-naïve patients, with the same titration schedule as recommended for oral administration. However, the concerns regarding administration in patients at risk for serious cardiac events would apply in these patients (or any patient given IV LCM), just as they do in patient given LCM orally. In addition to labeling and postmarketing surveillance, a REMS should address the effects on cardiac conduction, syncope, potential multi-organ hypersensitivity reactions, and the risk of suicidality.

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/s/

Sally Yasuda
7/7/2008 08:59:59 AM
BIOPHARMACEUTICS
Sally Usdin Yasuda; Safety Team Leader; Neurology Drug Products

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 15, 2008

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products/CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products/CDER

To: Jackie Ware, Pharm.D.
Regulatory Project Manager
Division of Neurology Products/CDER

b(4)

Subject: DCRP consult to review the cardiac safety report contained in NDAs 22-253, 22-254 [redacted]

This memo responds to your consult to us requesting we review Schwarz Biosciences' assessment of the cardiac safety of administering its product, lacosamide, as summarized in section 5.3.5.3 of the eCTD for NDAs 22-253, 22-254 [redacted] DCRP received and reviewed the following materials:

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- Your consult dated 27 Dec 2007
- Section 5.3.5.3 of the eCTD, an 1145-page document dated 03 Aug 2007 entitled Cardiac Safety Report: Lacosemide. Other sections of the eCTD were selectively reviewed as needed to understand section 5.3.5.3. No primary data were reviewed.

BACKGROUND

Schwarz Biosciences has submitted the following NDAs for lacosamide:

- 22-253 for the use of lacosamide tablets as adjunctive therapy for partial-onset seizures in adults
- 22-254 for the use of lacosamide solution for infusion as adjunctive therapy for partial-onset seizures in adults

[redacted]

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- [redacted] for the use of lacosamide tablets as primary therapy of neuropathic pain associated with diabetic peripheral neuropathy.

Clinical Pharmacology

Lacosamide is a new chemical entity, a "functionalized amino acid," whose mechanism of action is unclear. It has linear pharmacokinetics with high bioavailability after oral dosing. Tmax after oral dosing is 0.5 hours to 4 hours post dose and has a terminal half-life of approximately 13 hours. Following twice-daily oral dosing, the plasma concentration increases with an accumulation factor of approximately 2.3. Steady-state plasma concentrations are achieved after 3 days of twice-daily administration. It displays little (<15%) binding of drug to plasma proteins. About 40% of parent drug is excreted unchanged in urine, much of the rest is a methylated metabolite which the sponsor asserts has no pharmacological activity. CYP 2C19 is a minor route of metabolism; poor and extensive metabolizers show similar exposure. Exposure is slightly higher in the elderly. Male and females show similar exposure. No dose adjustment appears necessary for patients with mild or moderate renal or hepatic impairment. No significant drug-drug interactions have been identified. The oral dose is limited to about — ng/d by dizziness, somnolence, and fatigue; up-titration over several days appears to improve tolerance. The draft PI states the recommended dose for treatment of diabetic neuropathic pain is "200 mg two times a day (400 mg/day)" and "total daily dosage should not exceed — ng." For treatment of partial-onset seizures, the PI states lacosamide "should be initiated with 50 mg, twice daily (100 mg/day)" and then titrated "to the maximum daily dose of — mg." b(4)

Nonclinical

In vitro electrophysiological studies suggest that lacosamide enhances the slow inactivation of sodium channels, without affecting fast inactivation, by attenuating the proportion of available channels in a time- and voltage-dependent manner. This may lead to a reduction of sodium channel long-term availability reducing upstroke velocity of the action potential and slowing conduction velocity.

Nonclinical studies in dogs and monkeys demonstrate that administration of lacosamide results in:

- Dose dependent decreases in systemic blood pressure beginning at plasma concentrations of 11.3 to 22.6 µg/mL, within the range of plasma levels found in humans after the — 300 mg twice daily (14.5 ± 1.7 µg/mL). Lacosamide was not observed to lower systemic vascular resistance so the sponsor surmises that its hypotensive effect is most likely a result of a cardiodepressant effect. Dose dependent reductions in cardiac output were observed. b(4)
- Increases in heart rate at all dose levels
- Dose dependent increases in the PR interval and QRS duration. These increases occurred at plasma concentrations similar to those found in humans after the maximum recommended dose. Atrial conduction was affected at lower doses than ventricular conduction. At high doses (15-45 mg/kg), AV block, AV dissociation and nodal rhythm were observed. AV dissociation was accompanied by marked reductions in blood pressure and cardiac output.

John Koerner, a DCRP pharmacology-toxicology reviewer, had the following comments about the nonclinical evaluation of lacosamide:

"Nonclinical cardiac safety pharmacology studies show that lacosamide inhibits the human cardiac sodium current (IC_{50} values range from 67 to 293 µM), which can account for QRS widening in nonclinical and clinical studies. The desmethyl-metabolite (SPM 12809) also

inhibits the human cardiac sodium current by 20% at 100 μM, the highest concentration evaluated. Sodium channel inhibition with both parent and metabolite was voltage-dependent, since it was greater in more depolarized cells, which suggests that QRS widening might be more pronounced in ischemic than in well perfused hearts.

Consistent with inhibition of the human cardiac sodium channel, lacosamide reduced maximum upstroke velocity and shortened action potential duration in a concentration-related manner in canine Purkinje fibers (15, 50 and 150 μM) and ventricular myocytes (10 μM). Lacosamide inhibited the sodium current in isolated human atrial myocytes in a voltage dependent manner: IC_{50} of 67 μM at a holding potential of -70 mV.

AV block and sinus bradycardia in patients is consistent with transient depression of AV conduction and reduction of arterial blood pressure, cardiac output and cardiac contractility (+/- dP/dt) in nonclinical safety pharmacology studies in animals. The mechanism of these effects has not been evaluated thoroughly, although SCN5A (human cardiac sodium channel) mutations that produce functional effects on ionic current dynamics can lead to AV nodal conduction block, and sodium channel blockade can have negative inotropic effects.[1,2] Lacosamide does not inhibit L-type calcium channels at concentrations up to 500 μM. Nor does it inhibit hERG tail current at concentrations up to 3000 μM. Lacosamide has not been adequately tested for effects on adrenergic, muscarinic or adenosine receptors, since the highest concentration tested for binding was 10 μM, which is considerably lower than concentrations needed for interaction at the presumed target receptors, and for inhibition of cardiac sodium channels seen in nonclinical safety pharmacology studies. Additionally adequate pharmacology studies evaluating functional interactions of lacosamide with these and other receptors have not been performed."

Reviewer's comment: The voltage dependent inhibition of sodium channels is of concern because the prevalence of coronary artery disease is high in the diabetic peripheral neuropathy population. These patients are at risk for symptomatic and asymptomatic myocardial ischemia, which apparently potentiates the effects of lacosamide on sodium channels. Additionally, the class of local anesthetic (IA, IB or IC) to which lacosamide belongs has not been characterized; this may impact lacosamide's potential for ventricular proarrhythmia.

Clinical

A total of 3639 subjects participated in 49 phase 1 to 3 clinical studies of lacosamide. A total of 1338 unique subjects were exposed to oral lacosamide in 11 Phase 2/3 studies of subjects with partial-onset seizures. A total of 199 subjects with partial-onset seizures were additionally exposed to lacosamide solution for infusion. A total of 1628 subjects with neuropathic pain (1566 with diabetic neuropathic pain, 25 with mixed neuropathic pain, and 37 with post-herpetic neuralgia) were exposed to oral lacosamide. 994 of the subjects with partial-onset seizures and 1023 of the subjects with neuropathic pain were exposed during phase 2/3 randomized, double-blind phase2/3 trials. The entire clinical development program consisted of the following studies:

- 25 Phase 1 studies

[1] Wang et.al. Clinical, genetic and biophysical characterization of SCN5A mutations associated with atrioventricular conduction block. Circulation. 2002; 105: 341-346

[2] Schlepper M. European Heart Journal,. 1989: 10 (Suppl E): 73-80.

- 6 completed and 3 ongoing Phase 2/3 trials for adjunctive treatment for subjects with partial-onset seizures (using oral formulations)
- 2 completed Phase 2/3 trials for adjunctive treatment for subjects with partial-onset seizures (using solution for infusion)
- 6 completed and 3 ongoing Phase 2/3 trials for the treatment of subjects with diabetic neuropathic pain
- 2 completed Phase 2/3 trials for the treatment of subjects with post-herpetic neuralgia
- 1 completed and 1 ongoing Phase 2/3 trial for the treatment of subjects with mixed neuropathic pain

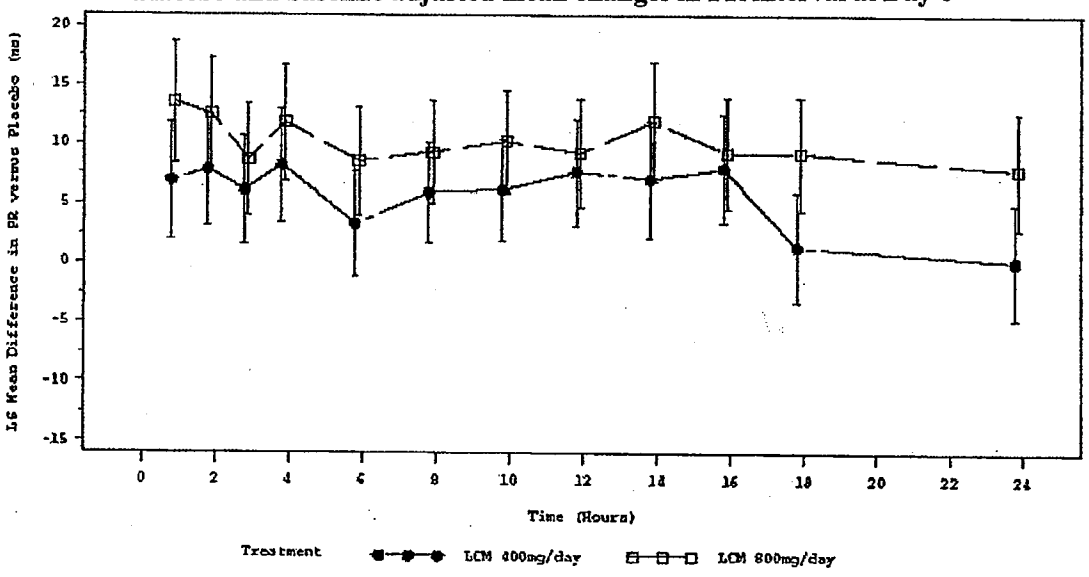
SPONSOR'S SUBMISSION

Study SP640

The sponsor conducted a "Thorough QT/QTc" study of lacosamide, protocol SP640. Because nonclinical and clinical data indicated that lacosamide administration with associated with lengthening of the PR interval, the sponsor explored the effect of lacosamide on the PR interval in SP640. The effects on QRS duration and heart rate were also investigated. SP640 was a randomized, placebo-controlled, parallel study, in which healthy subjects were administered oral doses of lacosamide 400 mg/day, lacosamide 800 mg/day, or placebo for six days (there was also a moxifloxacin arm). 12-lead ECGs were collected at baseline (day -1) then again at day six 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 hours post dose. Blood was obtained for determination of lacosamide plasma concentrations at the same time points.

As expected, administration of lacosamide resulted in lengthening in the time-matched PR interval as compared to baseline and adjusted for placebo over the 24 hour period after administration on day 6. The following figure from the sponsor's study report summarizes the data:

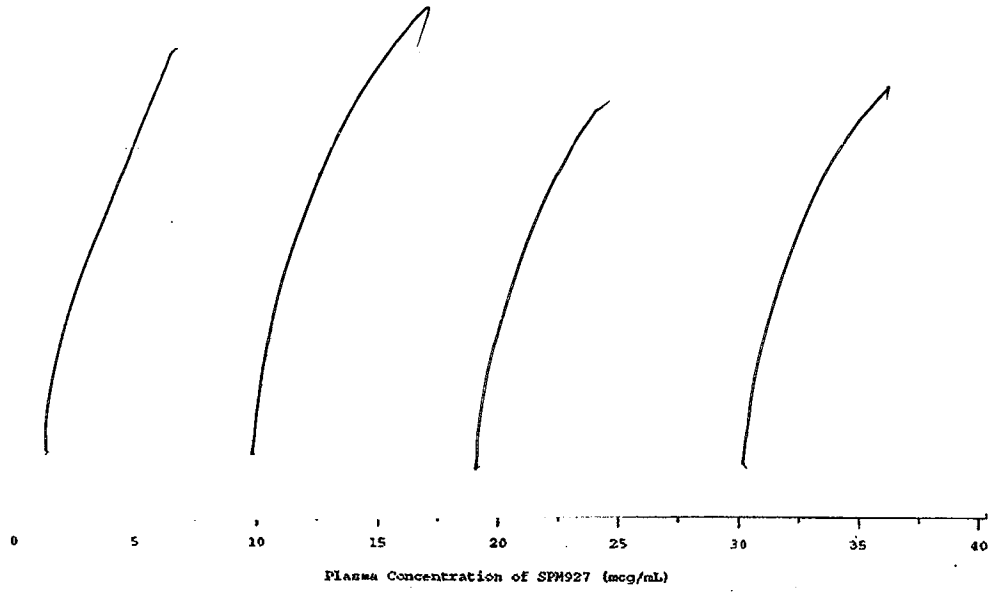
Placebo and baseline adjusted mean changes in PR interval at Day 6



The peak effect on the PR interval occurs at the time of expected Cmax, consistent with a dose response relationship. The upper 95% CI for the time matched change in PR interval from baseline and adjusted for placebo was 18.6 ms. The following figure from the sponsor's study report that correlates placebo and baseline adjusted PT intervals with plasma concentrations of lacosamide also makes clear there is a concentration dependent effect on the PR interval:

Sponsor Correlation of time-matched change from baseline in PR interval and plasma concentration of lacosamide

b(4)



As would be expected, an outlier analysis indicates that the frequency of the healthy subjects in this study developing AV block was dose related, as is indicated in the following table summarized from the sponsor's study report:

Subjects in Study SP640 with first degree AV block on Day 6

	> 200 ms	> 220 ms	> 250 ms
placebo	0	0	0
Lacosamide 400 mg/day	1/56 (3.6%)	1/56 (3.6%)	0
Lacosamide 800 mg/day	7/52 (13.5%)	3/52 (5.8%)	1/52 (1.9)

b(4)

Comment: Lacosamide prolongs the PR interval in a dose and concentration dependent manner. It appears that a dose not much higher than the [redacted] dose of 600 mg a day can result in PR interval prolongation of nearly 20 ms in healthy subjects. More marked PR interval prolongation could occur in subjects with pre-existing cardiac disease.

The other studies in the clinical development program are not as useful as SP640 in evaluating the mean effect of lacosamide on the PR interval. The intensity ECG acquisition in these studies is lower and the timing of ECG acquisition less well controlled so they can not be as informative. They are likely to underestimate the mean effect since ECGs are unlikely to have been obtained at the time of maximal effect. However, they may be useful in trying to evaluate the clinical significance of the effect on the PR interval.

Additionally, no effects on the QRS duration were detected in study SP640. Correlation of change in heart rate from baseline with plasma concentration suggests a concentration dependent effect of lacosamide on heart rate. The mean heart rate increased about 8 bpm from baseline and adjusted for placebo at T_{max} in the lacosamide 800 mg/day group.

Healthy subject studies
Among the 639 healthy subjects exposed to lacosamide in 24 clinical pharmacology trials, four (0.63%) had PR prolongation or AV block reported as an AE whereas none of 140 placebo subjects did.

Partial-onset seizure trials

- First degree AV block and PR prolongation were reported as an AE in four (0.4%) and one (0.1%) of subjects exposed to lacosamide in placebo controlled trials, but were not reported in the placebo group.
- No episodes of second degree AV block are reported
- The sponsor reports 15 subjects had AEs that could be consistent with syncope; four in placebo controlled trials and eleven in open label extension trials. Review of sponsor supplied narratives does not suggest that any were related to high degree AV block and, in those instances where the sponsor reports ECG findings, no abnormalities are noted. Only three of the 15 subjects withdrew due to the events.
- Eight subjects died. Four died due to noncardiac causes. Four deaths were sudden and all were attributed to sudden unexpected death in epilepsy. All four subjects who died suddenly were taking lacosamide in open label extension studies at the time of death. ECGs are reported for one subject and were not abnormal.

Diabetic neuropathy trials
Placebo controlled trials

- 1350 patients were enrolled in 4 placebo controlled trials; 1023 were randomized to lacosamide in doses of 200 - 600 mg/day in two equally divided doses for four to twelve weeks and 292 were randomized to placebo. Patients with recent MI, cardiac dysfunction, abnormal heart rates, second or third degree heart block were excluded. ECGs acquired a few times two to four hours after dosing.
- The mean maximum recorded increase in PR interval (i.e., mean of the maximum increase in PR interval recorded anytime during the treatment phase of the study) in subjects exposed to lacosamide 600 mg/day (n = 360) was 19.5 ms with a SD of 17.0 ms (versus mean of 9.7 ms for placebo).
- There was a trend toward an increase in mean maximum recorded increase from baseline in PR interval in older subjects.
- PR prolongation and first degree AV block were reported as an AE in four (0.4%) and five (0.5%) of subjects exposed to lacosamide compared to none in the placebo group.
- Two subjects had second degree block reported. In one, the episode occurred five days after administration of lacosamide had ended. In the other, second degree block was present at

baseline.

- One subject (12725 in trial SP742), a 54 yo male with baseline PR interval 230 ms, developed a nodal rhythm of 47 bpm after 43 days of lacosamide 200 mg bid. None of the reported concomitant medications affect AV nodal function. Although no symptoms are mentioned in the sponsor supplied narrative, the abnormality was noted during an unscheduled visit so it is likely that some symptom prompted the subject to seek medical attention. The subject was discontinued from the trial.

Comment: The sponsor assertion about the timing of these events should be verified by review of the CRF if possible.

- AV block was not reported as an SAE in any subject
- Atrial fibrillation and atrial flutter were reported as an AE in four (0.4%) and two (0.2%) of the subjects exposed to lacosamide compared to none in the placebo group.
- Syncope, loss of consciousness, and depressed level of consciousness were reported as an AE in 14 subjects exposed to lacosamide (1.4%) compared to none in the placebo group. Six of these subjects were discontinued as a result of syncope. The sponsor supplied narratives for three of the subjects suggests that the syncope was noncardiac; they were being administered 100, 200, and 400 lacosamide mg qd. Two of the other eleven were administered 400 mg qd, four 500 mg qd, and five 600 mg qd. The sponsor supplied narratives do not rule out a cardiac etiology in these cases. In fact, the sponsor attributes three of these episodes to cardiac causes. However, in none of the episodes does the sponsor report any definite associated ECG abnormality other than atrial flutter in one instance.

Comment: There is a rather striking imbalance in the occurrence of syncope in the placebo controlled trials in diabetic neuropathy that appears to be dose related. The cause of syncope is unclear. Syncope may have many etiologies. This reviewer has not reviewed CRFs, but can if they are particular ones that DAARP would like reviewed.

- 6 subjects died. 3 deaths were due to suicide or cancer. Three were potentially cardiac related. No important changes from baseline ECG for any of these subjects were noted.

Open label extension studies

905 subjects were exposed to lacosamide at doses ranging from 100 to 600 mg qd for more than 6 months and 735 for more than one year.

- 18 had PR prolongation or first degree AV block reported as an AE.
- One 59 yo female subject (#172707 in study SP745) developed asymptomatic Mobitz type 1 second degree AV block 297 days after beginning lacosamide 200 mg bid The subject was taking atenolol and had first degree AV block at baseline (PR interval > 300ms). She was withdrawn from the study due to this AE.
- 14 subjects had syncope, loss of consciousness, or depressed level of consciousness reported as an AE.
- 4 subjects had atrial fibrillation or flutter reported as an AE.
- 6 subjects died. 3 deaths were due to suicide or cancer. Three were potentially cardiac related. No important changes from baseline ECG for any of these subjects were noted.

All trials in diabetic neuropathy

- 43 subjects exposed to lacosamide (2.7% of the total subjects enrolled) had treatment emergent PR intervals > 250 ms during at least one EKG. A majority (28) had first degree AV block at baseline and tended to be older (35% ≥ 70 years old). 12 of the subjects with treatment emergent PR intervals > 250 ms were discontinued from placebo controlled trial, although only one of these was for high degree AV block.

Other neuropathy trials

One subject administered 300 mg bid in a R, DB, PC study of lacosamide administration for treatment of post herpetic neuralgia was hospitalized for syncope. He had first degree AV block on baseline ECG with a PR interval of approximately 240 ms. Telemetry during hospitalization revealed intermittent second degree AV block (Mobitz type not reported).

Sponsor suggested product label

[redacted] b(4)

DCRP COMMENTS

- Lacosamide administration results in a concentration dependent prolongation of the PR interval. The upper 95% CI for the mean effect in healthy subjects in after a dose of 400 mg bid is 18.6 ms. As might be expected, the effect appears to be somewhat greater in patients with underlying cardiac disease and probably is age dependent.
- PR prolongation and resulting first degree AV block in itself is unlikely to be clinically important in patients without AV nodal dysfunction, as evidenced by a lack of clinical adverse events that appear to be related to PR prolongation in the clinical program in such subjects.
- However, in patients with pre-existing AV nodal disease and/or being co-administered agents that block the AV node, PR prolongation by lacosamide may be clinically important. In such patients obtaining an ECG after lacosamide is titrated to steady state may be prudent.
- The voltage dependent inhibition of sodium channels by lacosamide is concerning because it suggests that myocardial ischemia will potentiate the effects of lacosamide on sodium channels. The prevalence of coronary artery disease is high in the diabetic peripheral neuropathy population and so symptomatic or asymptomatic myocardial ischemia is likely to occur frequently. The design of the clinical program minimized the information available about the effects of cardiac ischemia on AV block because patients with recent MI and cardiac dysfunction were not eligible to enroll.
- The sponsor proposed labeling [redacted] b(4)

[redacted] c. Clinically significant AV block is more likely to occur in patients who have preexisting AV block, are on concomitant medications that prolong the PR interval,

and/ or older. Preclinical data suggests that myocardial ischemia may potentiate the effect of lacosamide on the PR interval.

- Only subjects administered lacosamide in the placebo controlled studies of diabetic neuropathy developed atrial fibrillation or flutter. A study published this month (*Circulation* 2008; 117:1927) demonstrates an increased frequency of cardiac sodium channel variants in patients with atrial fibrillation suggesting that changes in sodium channel function may predispose to atrial fibrillation. Although the numbers were small, lacosamide administration may predispose to atrial arrhythmias.
- Syncope occurred much more frequently in subjects administered lacosamide in placebo controlled trials, especially in the diabetic neuropathy trials. Review of the sponsor supplied narratives does not suggest that PR prolongation is playing a role. If the review division has other data they would like reviewed, we would be happy to do so.

Thank you for requesting our input into the evaluation of the NDAs for this product. We welcome more discussion with you now and in the future.

APPENDIX

Highlights of Clinical Pharmacology

Therapeutic dose	The daily dose is administered in two equally divided doses. The recommended starting dose is 100 mg per day, which should be increased to an initial therapeutic dose of 200 mg per day after one week. Based on individual patient response and tolerability, the dose can be further increased by 100 mg per day every week, to a maximum recommended dose of — mg /day.	
Maximum tolerated dose	The maximum tolerated dose in clinical pharmacological trials was 800mg (400mg bid) in multiple dose trials (SP588, SP640) and 600mg in a single dose trial (SP587). The no-observed-adverse-effect-levels (NOAELs) were 60, 90 and 10 mg/kg/day in mice, rats and dogs after once daily oral administration of lacosamide for 3, 6 and 12 months.	
Principal adverse events	The most frequent AEs that lead to drop-out or withdrawal of the Informed Consent were dizziness, nausea and vomiting in a dose-dependent manner. These AEs were regarded as dose limiting.	
Maximum dose tested	Single Dose	800mg
	Multiple Dose	500 bid for 13.5 days (limited tolerability)
Exposures Achieved at Maximum Tested Dose	Single Dose (sd)	SP587 (800mg sd, N=9): C_{max}: Mean: 18.43µg/ml (26%) [Geometric Mean, CV%] $AUC_{0-\infty}$: Mean: 293.24µg/ml*h (26.5%) [Geometric Mean, CV%]
	Multiple Dose (md)	SP588 (500mg bid, N=4): C_{max}: Mean: 15.25µg/ml (1.78-21.80) [Median, range] AUC_{0-12}: Mean: 130.39µg/ml*h (14.89-196.26) [Median, range]
Range of linear PK	Dose-proportional increase of C_{max} and AUC for doses between 100mg and 800mg single dose and 100mg and 400mg multiple dose	
Accumulation at steady state	Following twice-daily dosing, lacosamide plasma concentration increases with an accumulation factor of approximately 2.3.	
Metabolites	1. Lacosamide (approximately 40% of the administered dose excreted unchanged) 2. SPM 12809 (approximately 30% of the dose) 3. Polar fraction (approximately 20% of the dose)	

b(4)

	4. Small amounts of further metabolites (p-hydroxy-, O-desmethyl-p-hydroxy-, O-desmethyl-m-hydroxy-, and desacetyl-derivatives of LCM) representing 0.5% to 2% of the dose were also found in urine. 5. N-carbamoyl-O-ß-D-glucuronide of the desacetyl-metabolite	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability of the oral formulation: Approximately 100%
	Tmax	• Lacosamide - Median (range): 1.00h (1.00-4.00h) [SP640, N=57, after 400mg/day at steady state] • SPM 12809 - Median (range): 12.00h (6.00-24.00h) [SP863, N=34, after 300mg sd]
Distribution	Vd/F or Vd	V/f - arithmetic mean ± SD : 1. 54.89 ± 14.08 L (SP587, after 400 mg sd oral lacosamide, N=12) 2. 48.92 ± 10.08 L (SP587, after 800 mg sd oral lacosamide, N=9) 3. 45.12 ± 9.45 L (SP588, after 300 mg sd oral lacosamide, N=14) 4. 57.11 ± 22.66 L (SP588, after 500 mg sd oral lacosamide, N=10)
	% protein bound	<15%
Elimination	Route	• Primary route: Renal excretion; 40% of dose is eliminated as unchanged lacosamide, 30% as SPM 12809 • Other routes:metabolism (Presumably hepatic, see SP642)
	Terminal t½	• Mean: 13 hours (CV: ~20%) for lacosamide • Mean: 19 hours (CV: ~20%) for SPM 12809 (SP620, after 100mg bid md in healthy male subjects)
	CL/F or CL	CL/f – Geometric mean (CV): 2.71 L/h (14.2%) [SP588, N=14, after 300mg sd] 2.40 L/h (14.2%) [SP588, N=12, after 300mg bid md]
Intrinsic Factors	Age	$AUC_{\tau,ss,norm}$*: ~ 25% higher AUC in elderly males (≥65 years) compared to young males (≤45 years), ~15% higher AUC in elderly females (≥65 years) compared to young males (≤45 years

		Cmax,ss,norm*: ~22% higher C_{max} in elderly males (≥65 years) compared to young males (≤45 years) ~25% higher C_{max} in elderly females (≥65 years) compared to young males (≤45 years) * body weight normalized
	Sex	AUCτ,ss: - 13% higher AUC in elderly females (≥65 years) compared to elderly males (≥65 years), after body weight normalization no differences in AUC between elderly females and elderly males $C_{max,ss}$: - 19% higher C_{max} in elderly females (≥65 years) compared to elderly males (≥65 years), after body weight normalization no differences in AUC between elderly females and elderly males
	Race	AUCτ,ss: - 10% higher exposure of LCM in Asian and Black compared to White subjects, but similar exposure after body weight normalization within the 3 ethnic groups $C_{max,ss}$: - No difference between Asian, Black and White subjects in mean $C_{max,ss}$
	Hepatic & Renal Impairment	<u>Hepatic Impairment</u> - AUCτ,ss, $C_{max,ss}$: 60%, 50% increased in subjects with moderate hepatic impairment, after body weight normalization the differences were reduced to 50%, 37% - The increase of exposure is mainly caused by coexisting renal impairment <u>Renal Impairment</u> $AUC_{(0-tz)}$: - 60% increased in subjects with severe renal impairment (differences were reduced by 10% by body weight normalization) - 20-30% increased in subjects with mild and moderate renal impairment (differences were reduced by 10% by body weight normalization)

		C_{max}: - 10-15% increase in subjects with mild, moderate and severe renal impairment
Extrinsic Factors	Drug interactions	<u>Phase 1 DDI studies:</u> **1. SP644 (Digoxin)** - No differences for AUC and Cmax of digoxin with and without coadministration of lacosamide - AUC and C_{max} of lacosamide under coadministration with digoxin were comparable to those obtained in previous trials without coadministration of digoxin (historical comparison) **2. SP660 (Metformin)** - Lacosamide: 6% increase of AUC, 8% increase of C_{max} under coadministration with Metformin - Metformin: No differences for AUC and C_{max} under coadministration with lacosamide compared to administration of metformin alone **3. SP601, SP602 (Valproic acid)** - Lacosamide: No differences for AUC and C_{max} under coadministration with VPA compared to administration of lacosamide alone - VPA: No differences for AUC and C_{max} under coadministration with lacosamide compared to administration of VPA alone **4. SP603, SP618 (Carbamazepine)** - Lacosamide: <10% increase of AUC and C_{max} under coadministration with CBZ compared to administration of lacosamide alone - CBZ: A maximum change of 10% of AUC and C_{max} under coadministration with lacosamide compared to administration of CBZ alone **5. SP863 (Omeprazole)** - Lacosamide: 10% increase of AUC and no change of C_{max} under coadministration with omeprazole compared to administration of lacosamide alone - Omeprazole: 10% increase of AUC and C_{max} under coadministration with lacosamide compared to administration of

		omeprazole alone **6. SP599 (Oral contraceptive)** - Ethinylestradiol: 10% increase of AUC, 20% increase of C_{max} under coadministration with lacosamide compared to administration of ethinylestradiol alone - Levonorgestrel: 10% increase of AUC and C_{max} under coadministration with lacosamide compared to administration of levonorgestrel alone - AUC and C_{max} of lacosamide under coadministration with ethinylestradiol and levonorgestrel were comparable to those obtained in previous trials without coadministration of both drugs (historical comparison)
	Food Effects	No differences in $AUC_{(0-tz)}$ and C_{max} in the fed state after a high-fat breakfast and in the fasting state.
Expected High Clinical Exposure Scenario	The most likely high exposure scenario will occur in the diabetic neuropathic pain patient with severe renal failure. The proposed labeling for lacosamide [redacted]	

b(4)

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Stephen Grant
4/15/2008 05:20:20 PM
MEDICAL OFFICER

John Koerner
4/16/2008 10:08:45 AM
PHARMACOLOGIST

Thomas Marciniak
4/18/2008 02:33:33 PM
MEDICAL OFFICER

Norman Stockbridge
4/21/2008 01:11:36 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-253 **Applicant: Schwarz** **Stamp Date: 9/28/2007**

Drug Name: Lacosamide Talets **NDA Type: Standard**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			OK. eCTD format-usable through the Global tool
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			" "
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			" "
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			Appears as so- limited sampling
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			OK. In PLR format. b(4)
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Clinical efficacy and safety submitted for epilepsy.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			But, seems rather cumbersome in the global format. Not a filling issue.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to	X			First study examined

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				200, 400 and 600 mg/day and identified the upper two doses as therapeutic without obvious increase in efficacy.
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 E2 Indication: epilspy Pivotal Study #2 E3 Indication: epilepsy	X			Along with the two phase 3 trials, the phase 2 dose ranging trial – may be adequate to support indication.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Yes
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Appears to conform
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Study SP-754 examined patients from the US. Study SP-755 examined patients from Europe with the majority (> 66%) being unconventional non-westerns European sites (Poland, Hungary, Lithuania). This is not an issue,
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			

b(5)

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			It is consistent with prior agreement.
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Deferral requested, once review is completed and a determination of cardiac safety in made. This is acceptable and consistent with previous discussions with this division.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			An abuse potential report is included.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See above (#17).
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

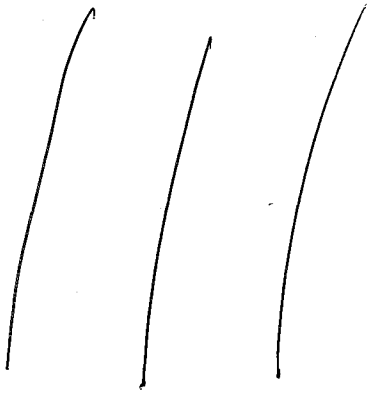
	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			General discussion of financial disclosure is provided. But, nothing by each investigator.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Identified in each individual clinical report.
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Recommended sites of inspection:

Centers for inspection are presented below, in the order of preference

For Study SP754:

Michael Sperling MD
Thomas Jefferson University Hospital
Jefferson Comprehensive Epilepsy
Center
900 Walnut Street, Suite 200
Philadelphia, PA 19107
Enrolled 22 with ITT of 18.



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CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Krauss, Gregory, MD
Johns Hopkins Hospital
600 N Wolfe Street
Meyer 2-147
Baltimore, MD 21287-7247
Enrolled 17 with ITT of 15.

For Study SP755:

b(5)

Dr. Zdravka Poljakovic
University Hospital Center Zagreb; Department of Neurology; Center for epilepsy
Kispaticeva 12, 10000 Zagreb, Croatia
Enrolled 20, 18 in ITT.

b(5)

Dr Sanja Hajnsek
University Hospital Center Zagreb; Department of Neurology; Center for epilepsy
Kispaticeva 12, 10000 Zagreb, Croatia
Enrolled 16, 16 in ITT.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Lourdes Villalba	11/21/07
Reviewing Medical Officer (Safety)	Date
Norman Hershkowitz	11/21/07
Reviewing Medical Officer	Date
Norman Hershkowitz	
Clinical Team Leader	Date

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

/s/

Norman Hershkowitz
11/21/2007 02:58:26 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 22-253, 22-254 —
Submission Number	000
Letter Date	September 28, 2007
PDUFA Goal Date	July 28, 2008
Primary Review Goal Date	May 27, 2008
Reviewer Name	Lourdes Villalba, M.D.
Review Completion Date	June 5, 2008
Established Name	Lacosamide
(Proposed) Trade Name	VIMPAT
Therapeutic Class	Anticonvulsant
Applicant	Schwartz Biosciences
Priority Designation	S
Dosing Regimen	200 — mg/day, oral tablet — — and IV solution for infusion
Indication	As adjunctive therapy in subjects with partial-onset seizures
Intended Population	16 years and above

b(4)

b(4)

Table of Contents

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b(4)

1 EXECUTIVE SUMMARY OF THE SAFETY REVIEW

1.1 Recommendation on Regulatory Action

Lacosamide is safe at doses of 200 to 400 mg daily. Recommendation for approvability is deferred until full evaluation of benefits and risks is complete (see review by Dr. Hershkowitz).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant proposes routine labeling and standard pharmacovigilance to address the risk of liver toxicity. For PR prolongation and associated cardiac events the sponsor proposes —— b(4)

The sponsor's proposal is insufficient to address the potential risk of heart conduction disorders, particularly in patients with pre-existent ECG abnormalities, arrhythmia, congestive heart failure and ischemic heart disease, most of whom have been excluded from these studies. b(5)

1.2.2 Required Phase 4 Commitments

None at this time.

1.2.3 Other Phase 4 Requests

Requests related to clinical safety will be discussed as part of the REMS.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lacosamide is a functionalized aminoacid that enhances the slow inactivation of sodium channels leading to reduction of the neuronal hyperexcitability characteristic of epilepsy. LCM is not marketed in any country. The sponsor proposes the use of LCM oral tablet — and intravenous infusion at doses of 200 to — mg daily, as adjuvant therapy in patients with partial onset seizures. b(4)

As of June 2007, 4012 unique adult subjects have been exposed to LCM (including all routes of administration, all indications and healthy volunteers). Of these, 1338 were in subjects with partial-onset seizures (1327 subjects from studies with the oral tablet) and 2001 in subjects with

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neuropathic pain. Of the subjects with partial-onset seizures exposed to oral LCM, 199 subjects also received IV LCM in Phase 2/3 trials.

The oral tablet database for the partial onset seizure indication consists of three multi-center, double-blind, randomized, placebo-controlled, dose-titration studies with a treatment phase and a tapering or transition phase, for a total duration of 18 to 21 weeks (SP667, SP774 and SP775), referred to as the **EP Pool S1** (with a total of 944 subjects randomized to LCM and 364 randomized to placebo); and five open label studies in patients with partial onset epilepsy which along with the placebo-controlled studies is referred to as **EP Pool S2** database (involving a total of 1327 subjects exposed to LCM). The interpretation of the safety results in this database is somewhat difficult because of the flexible-study design, with a fixed dose titration that allowed one step dose reduction during the titration phase.

The **IV infusion** database consists of one phase 2 and one phase 3 controlled studies (without placebo) in patients with partial onset epilepsy, and four phase 1 studies in healthy volunteers. The IV phase 2/3 studies were designed to evaluate the intravenous infusion as a temporary replacement for the oral formulation. Patients enrolled in the phase 2/3 studies had been previously exposed to oral LCM in the open-label epilepsy studies. SP616, was a two-day study, comparing the oral tablet (n=21) with the intravenous infusion (over 60 minutes [n=20] and 30minutes [n=19]) at doses of 100 to 300 mg bid. SP757, was a 5-day multiple dose study comparing three different infusion rates (30 minutes [n=40], 15 minutes [n=100] and 10 minutes [n=10]). Altogether, there were 199 patients with epilepsy exposed to LCM intravenous infusion. Overall, the number of unique subjects exposed to IV LCM including the phase 1 studies is 285.

The application also includes **21 phase 1 studies** in healthy volunteers with the tablet, capsule (n=2), and [redacted] formulations, including pharmacokinetic, drug interaction, special populations, a Through QTc study, and an abuse potential study. Altogether, the phase 1 oral studies involve 644 unique subjects exposed to LCM and 162 exposed to placebo. b(4)

LCM has been studied in 1939 subjects with painful diabetic peripheral neuropathy (DPN) (1566 subjects included in the original application and 373 from a study submitted with the safety update) and 62 were in subjects with other neuropathic pain conditions. The study design of these trials was similar to those in the epilepsy program. The analyses of safety in the DPN studies were also presented in a pool of placebo-controlled studies (DPN S1) and another for all studies (DPN S2). The safety of studies in neuropathic pain indications has been reviewed by Dr. Anjelina Pokrovnichka from the Division of Anesthesia, Analgesia and Rheumatologic Products (DAARP). My review will refer to safety findings identified in her review when these findings are different from those in the epilepsy population (particularly CV events and syncope).

1.3.2 Efficacy

LCM showed efficacy for the treatment of partial onset seizures at doses of 200 to 600 mg daily. The Efficacy of LCM is being reviewed by Dr. Hershkowitz.

b(4)

1.3.3 Safety

1.3.3.1 Safety with the oral formulation

One death occurred in the LCM treated group in the placebo-controlled pool (EP S1) (1/944= 0.1%). No deaths occurred in the placebo-treated group (0/364). Eight additional deaths occurred during the open label studies (with an overall rate of 0.7% in EP S2). Review of the cause of death did not reveal a pattern that suggests that they were drug related. There were 4 cases consistent with sudden death of epilepsy, all during the open label studies. The rate of SUDEP in this application is 0.002 per patient per year, which is similar to the reported rate of SUDEP with other antiepileptic drugs and in patients with severe, refractory epilepsy (0.005 per patient per year) [redacted] There was one death due to suicide. Suicidality is increased in patients with epilepsy as compared to the general population. The lifetime prevalence rate of suicide in the US is reported as approximately 1.1%. The average rate of suicide and suicide attempt in patients with epilepsy has been reported to be 11.5%. The rate of suicidality in the placebo-controlled database (one suicide, one suicide attempt and 3 suicidal ideation/thoughts as per my analysis) was 0.5% for LCM and 0.1% for placebo. This rate of suicidality with LCM is similar to that recently described with other AEDs. LCM should carry class labeling for suicidality.

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The mortality rate in the DPN controlled studies was 0.4% (4/1023) and 0% (0/291) on placebo. Eleven additional deaths occurred during the open label phase, with an overall mortality of 0.9% (15/1628). Causes of death were cardiac in 8 subjects, cancer in 5 subjects and suicide in 1 subject. Of the cardiac deaths, three occurred during the placebo-controlled studies (3/1023, 0.3% on LCM vs. 0% on placebo).

No deaths occurred in the phase 1, non-diabetic neuropathic pain studies and phase 2/3 intravenous studies.

The overall mortality rate in the LCM studies, including all formulations and indications is 0.6% (24/4012). The mortality rate in EP S1 + DPN S1 (placebo-controlled studies of at least 12 weeks duration) was 0.3% (5/1967) among patients randomized to LCM and 0% on placebo (0/655). Of the 5 deaths that occurred in the controlled studies, 3 were cardiac-related. Given the different exposure of LCM and placebo treatment groups definitive conclusions can not be drawn regarding whether LCM increases the risk of cardiac-related death.

The rate of treatment emergent (TE) serious adverse events (SAEs) in placebo-controlled trials for epilepsy (EP S1) during the treatment phase was 6.5% of all LCM-treated subjects as compared to 3.8% of subjects on placebo. The most frequently reported TE SAEs in this population were in the MedDRA Nervous System disorders system organ class (SOC) (2.1% for LCM and 1.6% for placebo-treated patients). The most frequent preferred term (PT) for SAEs was convulsion for both LCM and placebo-treated patients (0.8% each). The overall incidence of SAEs in all LCM treated patients was greater in EP Pool S2 (17.9%) than EP Pool S1 (6.5%). This is not unexpected given the longer duration (exposure up to 5 years) in EP Pool S2. The most frequent PT was again convulsions (7.9%), followed by dizziness (2.9%).

Most frequent TE SAEs in the DPN population belonged to the cardiac disorder system SOC (angina, coronary artery disease, A-fib, A-flutter, and bradycardia) and the nervous system disorder SOC (loss of consciousness and transient ischemic attack). Overall, SAEs were slightly higher in the LCM treated patients (7.5%) compared to the placebo (5.2%). There was evidence for dose dependency. The frequency of the cardiac SAEs was similar between the LCM and placebo treated patients (2.5% vs. 2.9%, respectively). However, most of the cardiac conduction/rhythm abnormalities recorded as SAEs were reported from subjects treated with LCM. Other significant adverse events that were observed to occur more frequently in patients receiving LCM compared to placebo were syncope related events (7.3% vs. 2.4%, respectively). Eight cases of serious syncope/loss of consciousness occurred in the neuropathic pain population. All of them were thought to be drug related. Four of these cases occurred at the 600 mg/day dose. Most cases did not have ECG evaluations at the time or after the event.

The rate of dropouts due to TE AEs in EP S1 during the treatment phase was 17.1% for LCM and 4.9% for placebo, with strong evidence of a dose response (8.1%, 17.2%, and 28.6% discontinued due to AEs from the LCM 200, 400 and 600 mg/day randomization groups, respectively). Most dropouts occurred during the titration period, particularly for the LCM 400 and 600 mg/day doses. The most frequent events were in the MedDRA Nervous system disorder System Organ Class (SOC) (9.9% for overall LCM and 2.5% on placebo, but 21.7% for LCM 600). The most frequent PTs leading to dropout were dizziness (0.6%, 0.4%, 4.2% and 17.2% in the placebo, LCM 200, LCM 400, LCM 600, respectively) and ataxia (0, 0.4%, 1.3%, and 5.4% in the placebo, LCM 200, LCM 400, LCM 600, respectively). Convulsion was the third most frequent PT leading to dropout, although the overall rate was similar for LCM and placebo (1.1% for both). Other AE that led to early dropout were nausea, vomiting, diplopia, blurred vision, and fatigue. All these AEs also showed a strong evidence of a dose response by randomization dose. The overall rate of dropouts in the long-term exposure dataset (EP S2) (18.3%), was similar to that of EP S1 (17.1%). Similar events led to dropout in the DPN population.

The most common adverse events in EP S1 were in the Nervous system disorders followed by GI disorders (nausea and vomiting), Eye disorders (diplopia, blurred vision) and General disorders and administration site condition disorders (mostly fatigue) SOCs. In the Nervous system disorders SOC, dizziness was the most common AE, presented by 8.2%, 15.9%, 29.5% and 52.7 % of patients randomized to placebo, LCM 200, 400 and 600 mg/day, respectively. The second most common events belonged to the Cerebellar and coordination disorders high level term (HLT) that includes preferred terms such as ataxia, nystagmus and balance disorder. These adverse events are known to be associated with AEDs. Common events in the DPN population were similar to those in the epilepsy population

Routine laboratory evaluations (chemistry, hematology laboratory measurements and urinalyses) did not reveal issues of clinical concern in patients with partial-onset seizures or healthy volunteers, except for a slightly higher percentage of outliers for ALT elevations (0.7% on LCM vs. 0% on placebo). One healthy volunteer developed hepatitis and nephritis after completion of a LCM oral study, but the bilirubin is not available for this patient at the time of these events.

In general, mean changes in pulse rate, systolic and diastolic blood pressure (SBP and DBP, respectively) and weight were small across all LCM treatment groups, and were not different

from placebo at doses of 200 to 600 mg daily. Outlier analyses for SBP and DBP showed a similar percentage of patients having increased or decreased outlier values at least once during the study. In SP640, the TQTc study with the oral tablet in normal volunteers showed an increase from baseline in mean SBP (8.6 mmHg), mean DBP (10 mmHg) and mean pulse (2 bpm, as compared to -6 for placebo) at the at the 800 mg/day dose, but not at the 400 mg/day dose.

After evaluating the abuse related data submitted in the NDA, Controlled Substance Staff (CSS) concluded that LCM has abuse potential similar to that of alprazolam and should be Schedule IV drug class under the Controlled Substances Act (CSA).

Based on non-clinical safety, early phase 1 data and class effects, some AE were identified as being of special interest. A summary of the results for selected AEs is presented as follows:

1) ECG, cardiac and potentially cardiac disorders including syncope
2) Liver toxicity
3) Seizure
4) Rash and hypersensitivity
5) Psychosis and memory impairment

1) ECG, cardiac and potentially cardiac disorders, including syncope

There is evidence that LCM has a dose-related effect in the heart conduction system, particularly the PR and QRS interval. The mean maximum change in PR for LCM as compared to placebo was 1.5ms, 3.1ms, and 4.5ms in the LCM 200, LCM 400 and LCM 600 groups, respectively. Regarding the QRS, there was a slight mean increase from Baseline (approximately 2ms at the end of the titration and maintenance Phases) in the LCM 600mg/day treatment group. The difference with the mean maximum QRS increase on placebo was -0.9ms, 0.5ms, and 0.4ms for the LCM 200, LCM 400, and LCM 600mg/day groups, respectively. There were no substantial differences with placebo in the mean or median duration of the QT, QTc Bazett (B) and QTc Fredericia (F) intervals at the end of the titration, maintenance or taper period. Interpretation of the ECG data over time in EP S2 showed no relevant findings but it was limited by the progressively decreasing number of subjects at the later time point.

Analyses of ECG morphology in EP S1, based on manual central ECG over-reading for SP754 and SP755 shows that the frequency of abnormal ECG findings was generally similar for LCM and placebo, except for the finding of ventricular-related conduction abnormalities, particularly broad QRS, with or without intraventricular block and complete or incomplete right bundle block with LCM (12% for LCM 600 mg and 3% for placebo).

In EP S1 there were four adverse events of first degree AV block in the LCM group (0.5%) - one of which required withdrawal- and no cases on placebo. There were no reported cases of second degree AV block or serious arrhythmia. This population was young (mean age around 40 years, with only 18 patients being >65 years) and healthy (very few patients had an underlying cardiovascular disease). In DPN S1 (a population with higher cardiovascular risk) there were 5 adverse events of first degree AV block (0.5%), 1 of second degree AV block, 4 of atrial fibrillation, 3 of atrial flutter and one nodal rhythm, all in the LCM treatment group. These

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events appeared to be dose and concentration dependent. No such cases were observed on placebo in DPN S1.

Eleven cases of treatment emergent syncope/loss of consciousness were identified in the epilepsy population, three of them in the controlled phase (two on LCM and one on placebo). Twenty seven cases of syncope were identified in the neuropathic pain population, 13 of them during the controlled studies (all in the LCM treatment group) and 14 in the open label studies. Overall, the rate of syncope in the controlled phase of the epilepsy and neuropathic pain studies was 0.8% for patients randomized to LCM (15/2004) and none of the patients randomized to placebo (although one patient was on placebo at the time of the event in the extension study). Four subjects presented syncope during the phase 1 studies. The rate of syncope including all LCM studies is 1.2% (42 cases among 3639 subjects who received LCM). The numbers indicate that LCM is associated with an increased risk of syncope as compare to placebo, particularly in the neuropathic pain population, however, the mechanism is unclear. Most patients did not have ECGs or measurements of orthostatic blood pressure at the time of (or closely after) the syncope.

A Thorough QT study (TQT)(SP 640) was conducted in healthy volunteers at doses of 200 to 800 mg daily. Upon extensive evaluation of this study, the FDA QT Team found no QT/QTc prolongation effects. Analysis of central tendency in this study showed a dose-related increase in heart rate and PR interval. The maximum mean changes in PR interval on Day 6 (steady-state) were observed at 1 hour post-dose and were 6.3ms, 13.6ms, and 18.2ms in the placebo, LCM 400, and LCM 800. The changes in heart rate were similar for placebo and LCM 400, but LCM 800 was associated with a mean increase from baseline of approximately 5 bpm. The rate of QRS≥ 100 ms in this study was 29.6% for placebo, 50% for LCM 400 and 42.3% for LCM 800, suggesting that LCM prolongs the QRS interval. No subject in any treatment group had a QRS duration >120ms during the treatment phase. There was no evidence of orthostatic hypotension in this study.

In summary, LCM was associated with dose-related PR prolongation and first degree AV block in all populations studied. In the neuropathic pain population, second degree AV block, atrial fibrillation & flutter were also observed. The overall rate of syncope/loss of consciousness in the LCM program was 1.1%. The mechanism of the syncope was not clear in most cases but in the absence of documented normal ECG, a cardiogenic origin can not be excluded. PR prolongation and resulting first degree AV block in itself is unlikely to be clinically important in patients without AV nodal dysfunction. However, in patients with pre-existing AV nodal disease and/or being co-administered agents that block the AV node (who were mostly excluded from these studies) PR prolongation by LCM may be clinically important. [redacted]

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2) Liver toxicity.

LCM at doses of 200 to 600 mg daily is associated slight transaminase (AST/ALT) and GGT elevation, as compared to placebo (2.4% on LCM, vs. 1.1% on placebo in EP S1). The rate of ALT/AST ≥3x ULN in EP S1 was 0.7% and 0% in the LCM and placebo groups, respectively. However ALT data were missing in 0.5% and 2.2% of LCM-treated and placebo-treated patients,

respectively. ALT/AST & GGT elevations were not associated with elevated bilirubin and were usually reversible upon drug withdrawal. No evidence of liver toxicity was observed in the DPN population. One healthy volunteer developed hepatitis and nephritis 10 days after completing LCM treatment. Bilirubin and prothrombin time were not available for this patient. This case was consistent with drug induced hypersensitivity. Liver toxicity may be addressed with labeling and routine pharmacovigilance.

3) Seizure

In non-clinical studies, seizure was the dose limiting toxicity and the cause of death. Evaluation of seizure-related AEs in this database is difficult because seizure was also the primary efficacy endpoint. LCM showed evidence of reducing the rate of seizures at doses of 200 to 600 mg daily. Based on clinical judgment some investigators considered an increase in seizure activity as lack of efficacy and others considered it an adverse event. Evaluation of AE of seizure in EP S1 (including convulsions, seizure, grand mal seizure, epilepsy and focal seizure preferred terms) during the treatment phase shows a similar rate of adverse events between overall LCM and placebo (3.9 % each), with the following rates: 3%, 4.5% and 4.3% for LCM 200, 400 and 600, respectively. An analysis of any dropout due to seizure (either lack of efficacy or adverse event) in EP S1 shows the following rates: 2.5% on placebo, 1.9% on LCM 200, 2.8% on LCM 400, 1.0% in LCM 600 and 2.1% for overall LCM. These analyses suggest that LCM does not increase the risk of seizures in patients with epilepsy. However, one case of seizure was observed in the DPN population while on LCM 400 mg/day, on relative study day 225. This case was thought to be possibly drug related. Three withdrawal seizures occurred in the LCM 400 group during the tapering phase and one during the maintenance phase, when LCM was discontinued due to elevated ALT/AST. The risk of withdrawal seizures warrants a statement in the WARNING & PRECAUTIONS section of labeling.

4) Rash and hypersensitivity

In EP S1 the rate of rash was similar between LCM groups and placebo (3.3% and 4.7%, respectively), although there was an increased rate of pruritus (2.6% on LCM and 0.5% on placebo). In DPN S1, the rate of rash was a little higher in the LCM group as compared to placebo (2.7% and 1%, respectively). There were no severe cutaneous skin reactions such as Steven-Johnson syndrome and toxic epidermal necrolysis in the entire database. There was, however, one case of hepatitis/nephritis drug hypersensitivity in one of the phase 1 studies. This multi-organ hypersensitivity reaction warrants mention in the WARNING & PRECAUTIONS section of labeling.

5) Psychosis and memory impairment

An analysis of the Psychiatric disorders SOC shows a rate of 17.1% for LCM and 9.4% for placebo. Three patients developed psychotic disorders while on LCM, as compared to none on placebo. The numbers are small to draw definitive conclusions. The HLGT terms that drive the difference in the rates of Psychiatric disorders between LCM and placebo are the "depressed mood disorders and disturbances" (3.6% and 0.5% for LCM and placebo respectively)) and "mood disorders and disturbances"(2.8% and 0.3%, for LCM and placebo respectively).

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Therefore there is evidence that LCM has some effects on mood. The individual PT with the higher incidence was depression (2.6% on LCM and 0.5% on placebo). Other PTs reported in EP S1 were crying, tearfulness, euphoric mood, mood altered, mood swings. Depression can be addressed through adequate labeling and routine pharmacovigilance.

In EP S1, AEs under the Nervous system disorders SOC, Mental impairment HLGT was observed in 2.7%, 1.5%, 5.3%, and 9.9% of patient randomized to placebo, LCM 200, LCM 400 and LCM 600, respectively. One hundred and nine additional patients had an AE under the MedDRA mental impairment disorders HGLT during the open label phase, at doses of 100 to 800 mg/day (overall, 11.9% of patients in EP S2). The interpretation is hampered by the lack of control and the use of multiple concomitant medications during the open label phase.

1.3.3.2 Safety with the intravenous formulation

Overall, there did not appear to be substantial differences in the safety of the oral and IV formulations, however, these studies were not powered to adequately address safety comparisons. From the pharmacokinetic point of view the IV 30-minute infusion and IV 60-minute infusion were bioequivalent to the oral formulation, and the exposure of the IV 15-minute infusion was 20% higher than that of the oral tablet in healthy volunteers. A 20% increase in exposure is unlikely to be of clinical significance, except in the elderly – who showed a 25% increase in LCM exposure as compared to non-elderly adults- and in subjects with underlying renal or hepatic impairment.

There were no deaths, and there were few serious adverse events with the IV formulation. In SP616 (two-day study, comparing 60 min vs. 30 min infusion, and to the oral formulation), 25% to 32% of patients had at least one AE. In SP757 (five-day study) the rate of AEs was 24% to 43%. The most common AE were in the Nervous system disorders SOC, followed by General disorders and administration site conditions (local irritation) and Eye disorders.

The following ECG related AEs were reported with the IV formulation: First degree AV block (n=2), right BBB (n=1), QTc prolongation (n=2) and profound bradycardia with a question of a sinus bradycardia versus AV block with sinus exit block (n=1)(rate: 5/285= 1.8%). Three of those patients dropped out because of these AEs (3/285= 1.1%). No remarkable changes were observed in laboratory parameters in these short studies with the IV formulation, except that in SP616, there seemed to be a higher rate of neutropenia <1500/L in the IV treatment groups (3/39=7.8%) as compared to the oral formulation (0/29). The clinical significance of this observation is unclear. Given the study design, comparison of AEs, ECG/laboratory and vital sign parameters between treatment groups in the IV studies is inappropriate.

Of note, only one patient older than 65 years and no patients younger than 18 years were included in the IV pool. Moreover, the epilepsy studies with intravenous LCM were conducted in patients who had been previously exposed to oral LCM for several weeks or months before being exposed to the IV formulation and were known to tolerate it well. In my opinion, IV LCM should not be given to naïve patients.

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1.3.4 Dosing Regimen and Administration

The applicant proposes to administer LCM orally, at doses of 200 to — mg daily in patients with partial onset seizures, of ages — years and above. The initial dose is 50 mg bid, with weekly increases, up to a total of — mg daily. The analysis of adverse events and dropouts to adverse events suggests a clear dose-response in terms of safety. In EP S1, 29% of patients discontinued due to AEs from the LCM 600 treatment group, as compared to 17% from the LCM 400 group. Most cases of syncope in the development program occurred at LCM doses of 600 mg/day. In the absence of a substantial efficacy advantage for LCM 600 mg/day over LCM 400 mg/day, I would recommend that the maximum recommended dose should be 400 mg daily.

b(4)

1.3.5 Drug-Drug Interactions

No clinically meaningful pharmakinetic interactions with studied antiepileptic drugs (carbamazepine, valproate), omeprazole, digoxin, and an oral contraceptive containing ethinlyestradiol and levonorgestrel were identified by the clinical-pharmacology reviewer.

1.3.6 Special Populations

Clinical Pharmacology studies were conducted in hepatically impaired and renally impaired patients. These studies showed increased exposure to LCM in both populations (approximately 50-60% for hepatically impaired and 60% for renally impaired). The Clinical Pharmacology reviewers recommend dose adjustment (approximately — of the maximum dose recommended in normal patients) for mild and moderate hepatic impairment as well as for severe renal impairment/ESRD patients. LCM should be contraindicated in patients with severe hepatic impairment.

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Clinical Pharmacology studies in the elderly showed a 25% increase in exposure as compared to non-elderly adults, after adjustment for renal function. No dose adjustment is required, however, caution should be recommended during dose titration in the elderly.

No studies were conducted in the pediatric population <16 years. The partial onset seizure studies included patients younger than 18 years, however, the number of patients who were 16 and 17 years old was small (only 3 were 16 years old and 4 were 17 years old).

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2 INTRODUCTION AND BACKGROUND

Lacosamide (LCM) also referred to as harkoseride, [R-2- [R]-2-acetamido-N-benzyl-3-methoxypropionamide or ADD 234037, is a member of a series of functionalized amino acids specifically synthesized as anticonvulsant drug candidates.

LCM enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner, leading to a reduction of sodium channel long-term availability which increases activation thresholds and reduces hyperexcitability of neurons characteristic of epilepsy. Other sodium channel modulators such as lamotrigine, phenytoin, and carbamazepine enhance fast inactivation with no or small effects on slow inactivation. Additionally, LCM interacts with collapsing response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth.

A more detailed background is provided in the efficacy review done by Dr. Hershkowitz.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

These findings are addressed in more detail in the efficacy review done by Dr. Hershkowitz.

3.1 Non-clinical safety pharmacology and toxicology.

Safety pharmacology and toxicology studies indicate pharmacodynamic (PD) effects of LCM on the CNS resulting in severe clinical signs, such as ataxia, abdominal and/or lateral position, tremors, and, at high doses, convulsions. Convulsions appear to be the cause of death in most cases of prematurely deceased animals and are considered dose-limiting in all species. Of note, a proconvulsant effect following high doses is seen with most, if not all, anticonvulsant drugs. Ataxia is also a common adverse effect seen with other anticonvulsants. There were no structural lesions associated with these neurologic symptoms.

In vitro investigations of the cardiovascular effects of LCM showed that LCM reduced the action potential duration in cardiac tissue and inhibited sodium current in isolated cells. In vivo studies showed decreased cardiac conduction. LCM induced short-lasting hypotensive effects with decreases in systolic left ventricular pressure and reduced cardiac output in anesthetized instrumented dog. These effects were accompanied by an increase in PR interval and QRS complex duration. These cardiac conduction and hemodynamic effects started at the time of peak plasma concentration after the IV infusion, at doses equivalent to the 300 mg bid dosing in humans. For details on the non-clinical safety results the reader is referred to Section 7.1.4.1 of this review and to the review by the FDA Pharmacology-toxicology reviewer.

The liver was identified as a potential target organ in toxicological studies with rats, but not with mice and dogs. Rats showed increased liver weight, liver enzymes, triglycerides and cholesterol.

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Non-clinical pharmacology findings are discussed in detail by the Pharmacology-Toxicology reviewers, Edward Fisher, Ph.D (DNP) and BeLinda Hayes, Ph.D. (DAARP).

Comment: Based on non-clinical studies, the sponsor identified liver and cardiac system as the main areas that needed follow up in the clinical program. Additionally, although CNS toxicity is known to be associated with AEDs, it deserves attention in this clinical program as LCM is going to be used as adjunctive therapy to other drugs that also have CNS effects.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The Clinical Data comes from studies conducted by the sponsor in 3639 subjects who participated in 49 clinical trials of LCM (Phases 1 through 3) as part as — different applications (NDA 22-253, -254 — Lacosamide is not marketed in any country; therefore there is no available postmarketing data. The overall exposure to Lacosamide in these —NDAs is presented in Table 1.

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Table 1. Overall exposure to Lacosamide as of 10/16/06

Formulation/population	Total number of unique exposures	
	LCM	Placebo
Oral formulation (tablet, capsule)		
Phase 1 – oral only[a]	644	162
Partial-onset seizures: EP Pool (tablet)	1327[b]	736[c]
Partial-onset seizures: SP586/SP598 (capsule)	13[b]	0
Diabetic Neuropathic Pain Pool	1566	291
Mixed neuropathic pain	25	0
Post-herpetic neuralgia	37	14
Total exposures to oral formulation (tablet, capsule)	*3610*	*1203*
Total person-years of exposure to oral formulation (tablet or capsule)	*3375.6*	*216.2*
Solution for infusion		
Phase 1 iv pool	86[d]	4
Partial-onset seizures: Phase 2/3 iv pool[e]	199	0
Total exposures to solution for infusion	*285*	*0*
Total person-years of exposure to solution for infusion	*2.0*	*0.01*
Total unique exposures[e]	**3639**	**1207**
Person-years of exposure[e]	**3377.6**	**216.2**

EP= Epilepsy. DNP=diabetic neuropathic pain; iv=intravenous; LCM=Lacosamide. [a] Includes study 903. [b]Two of these subjects rolled into SP615 in EP Pool S2; thus, 11 subjects in SP586/SP598 represent unique LCM exposures not counted in EP Pool S2. [c] The number of subjects randomized to placebo and those subjects randomized to LCM but received placebo during the initial weeks of the titration phase (ie, before starting LCM) are included. [d]Of the 86 subjects in the Phase 1 iv pool, 57 subjects also received oral LCM and are counted as a Phase 1-oral exposure above; 29 received only iv LCM and were thus unique LCM exposures for Phase 1 IV pool. [e] Based on all available data from visits completed as of 16 Oct 2006 (partial-onset seizures) and 15 Sep 2006 (pain). All subjects in the Phase 2/3 iv pool were also exposed to oral LCM and are therefore also counted as an exposure to oral LCM; placebo exposure for Phase 2/3 iv pool is not included as the subjects were concurrently receiving oral LCM and are counted as LCM exposure; the calculation of total person-years of exposure includes days of exposure to both oral and IV formulations. Source: April 16, 2008 submission in response to FDA request for information. (Original table in page 46 of the sponsor's Clinical Overview did not contain information for placebo).[1]

[1] Comment: Throughout the application, the sponsor used 781 as the denominator for "all patients exposed to placebo in EP S1" which is different from the n=736 included in Table 1, and includes patients who missed a dose

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The sponsor separated the LCM studies into groups or pools for analysis of safety. The studies included in each group are presented in the following table:

Table 2. Safety Pools for lacosamide

Safety Pools	Study number
Phase 1 studies (n=25)	SP619, SP657, SP658, SP645, SP600, SP835, SP587, SP836, SP588, SP834, SP620, SP643, SP661, SP641, SP642, SP644, SP660, SP601, SP602, SP603, SP618, SP863, SP599, SP640, SP903.
Phase 2/3 studies with oral tablet (n=19)	Epilepsy indication (EP) Pool S1: SP667, SP754 and SP755 (all placebo-controlled) Pool S2[1]: same above + SP607, SP615, SP756 & SP774 Diabetic Neuropathic pain (DNP) Pool S1: SP614, SP742, SP743 & SP768 (all placebo-controlled) Pool S2: same as above + SP665, SP745, SP746 and SP830 Other neuropathic pain conditions SP611, SP647, SP655 & SP690
Phase 2/3 studies with Solution for IV infusion	SP616 & SP757

[1] EP S2 does not include exposure to the oral capsule formulation (SP586 & SP598).

This review will cover the safety for NDA 22-253 (Lacosamide tablets), NDA 22-254 (Lacosamide IV infusion) [redacted]. I will focus on the safety in the phase 2/3 epilepsy studies (oral tablet and IV). I will also review the safety in the phase 1 studies and in the phase 2/3 studies with the oral capsule, which are not included in the ISS safety pool EP S1 or S2. The safety in the neuropathic pain studies is being reviewed separately by Dr. Prokovnichka (DAARP).

Summary of study designs

- **Phase 2/3 studies with oral tablet**

Briefly, there were three randomized, multi-center, placebo-controlled studies with a forced Titration phase up to a target dose of 200, 400 or 600 mg/day over 4-6 weeks, and a 12-week Maintenance phase, followed by a 2 or 3-week Transition phase (in which patients on placebo who accepted to enter the open label phase were titrated up to 200 mg daily) or a Taper phase (for those not going into the open label phase). The total duration of the studies was 18 to 21 weeks.

Of note, 1-step dose reduction was allowed once at the end of the Titration Phase (prior to the Maintenance Phase) in the event of intolerable AEs. If a second dose decrease was needed, the patient was supposed to be withdrawn from the study.

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of LCM while on the active treatment group. All tables of AE by dose at onset included in this review are based on the original sponsor submission and therefore use the n=781 denominator.

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COMMENT: The sponsor chose to present the analyses of the AE occurring in the "treatment phase" (titration and maintenance) separately from the transition and taper phases. This approach is reasonable, as the transition phase refers to placebo patients going into the open label phase and it would artificially increase the number of events in the placebo group. I would have included events that occurred during the taper phase along with the treatment phase, but the number of events during the taper phase is small and does not impact the overall conclusions from the safety in the treatment phase.

Because of the titration design, some events occurred at doses lower than the randomization group dose, or even while patients randomized to active treatment were still receiving placebo. The sponsor presented AE tables by randomization dose and by dose at onset of the AE. It is unclear what the best way to look at these events is. My review mostly shows analyses by randomization dose, although occasionally the analysis by dose at onset is also included.

Interpretation of the safety in the S2 pool is particularly challenging. The S2 pool includes subjects receiving LCM in the controlled phase as well as open-label extension and naïve subjects entering open-label studies. The open-label design allowed for multiple LCM and/or concomitant AED dose increases and/or decreases to achieve maximum seizure control for the subject. Addition of VNS, changes to VNS settings, or epilepsy surgery (ie., lobectomy) were also allowed and could also result in LCM dosing increases and/or decreases. The LCM exposure period for EP Pool S2 was over 1 year for >58% of subjects and greater than 3 years for >15% of subjects. Over the course of long-term treatment in the open-label extension trials, a subject may have experienced an AE multiple times that could result in multiple dose reductions (and ultimately early discontinuation) at different doses.

The sponsor used two approaches to the AE analyses: by modal dose (the dose most frequently used) and by dose at onset of the AE. Again, it is unclear what the best way to look at these data is. Throughout this review, AEs in the EP S2 pool will be presented mostly by modal dose, and occasionally by dose at onset. Both approaches are confounded by the above described factors.

Additional information regarding the studies design and eligibility as well as justification for the dose chosen for the phase 2/3 studies is presented in **Appendix 1** of this review.

COMMENT: Neuroleptics, MAO inhibitors, barbiturates, narcotic analgesics, anxiolytics, amphetamines, sedative antihistamines, thanquilizers, hypnotics as well as felbemate and vigabatrin were not allowed during the phase 2/3 clinical studies with Lacosamide. Calcium channel blockers and beta blockers were not specifically excluded but less than 5% of patients were taking these medications in EP S1. Other exclusion criteria of relevance are: confirmed clinical significant ECG abnormality and resting pulse <50 bpm or >110 bpm at visit 1.

A summary of phase 2/3 clinical studies of oral Lacosamide for the epilepsy indication is presented in Table 3.

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Table 3. Phase 2/3 clinical studies with oral Lacosamide for the partial onset seizure indication

Trial/ country	Design/ duration	Population	N Placebo	LCM (mg/day)			
				200	400	600	Any dose
Placebo-controlled							
SP667 US and non-US (Phase 2b)	Multi-center, DB, R, PC 8-week baseline phase	58% male Age 18-68	97	108	107	106	321
SP754 US only (Phase 3)	Up to 21-week treatment - 6-week forced titration* - 12-week maintenance - Either 2-week transition or 3-week taper phase	49% male Age 16-71	104	-	204	97	301
SP755 Non-US (Phase 3)	Multi-center, DB, R, PC 8-week baseline phase 18- week treatment - 4-week forced titration* - 12-week maintenance - Either 2-week transition or taper phase (dosing on a bid basis)	52% male Age 16-70	163	163	159	-	322
Total randomized in PC studies (Pool 1)			**364**	**271**	**470**	**203**	**944**
Open Label & extensions							
SP586[1] US	Single center, OL, ascending dose, 4 weeks (oral capsule)	3 F, 9M Age 23-50	200 to 600 mg/day				12
SP598[1] US	Multi-center, OL extension (oral capsule) Up to 621 days	1F, 7M Age 27-50	200-600 mg/day				8
SP607 US	Single center, OL (oral tablet)	44% male Age 18-63	100 to 600 mg/day				91
SP615 US & non-US[2]	Multi-center, OL exten. to SP598, SP607 & SP667; oral tablet, bid dosing, up to 8 years.	48% male Age 18-65	100 to 800 mg/day				370
SP756 US[3]	OL extension to SP754, Up to 4 years	52% male Age 16-70	100 to 800 mg/day				302
SP774, Non-US[4]	OL extension to SP755 Up to 4 years	55% male Age 16-68	100 to 800 mg/day				376
Total number of unique patients exposed to oral tablet (EP Pool S2[1])							**1327[5]**

N= number of patients randomized. LCM= Lacosamide. DB= double-blind. R=randomized. PC= placebo-controlled (patients receiving placebo are on background AED therapy). OL= open label. *Forced titration to dose to which patient was randomized; 1-step back titration was allowed at the end of the titration phase. [1]EP S1 and 2 pools do not include exposure to the oral capsule. Source: Sponsor's Table 1 of Summary of Clinical Safety in original application. [2;3,4] As of the cutoff date for analysis in the original submission (October 16, 2006) SP615 was ongoing for approx. 5 years, SP756 was ongoing for approx 2 years and SP774 was ongoing for approx 2 years

(information submitted at time of 120-day Safety Update). [5] Total exposure in EP S2 as of October 16, 2006 = 1696 PYRs.

Of note, the 120-day Safety Update Report (SUR), submitted in January 25, 2008, includes updated safety analyses to the S2 Pools for the partial onset seizure and neuropathic pain indications. The SUR reports that 85 out of 370 patients in SP615; 88 out of 302 patients in SP756, and 135 out of 376 patients in SP774, had been on placebo during the double-blind phase of the studies. As of the cut-off date of the original submission, the total exposure was 1803 PYRs. As of the cutoff date of the SUR (June 12, 2007), the maximum duration of treatment has been approximately 5 years and 10 months for SP615; 2 years and 9 months for SP756 and 2 years and 6 months for SP774. The total exposure to LCM as of June 12, 2007, in EP S2 is 1327 subjects (2088 PYRs of exposure) and in DPN S2 is 1939.

- **Phase 2/3 studies with IV formulation for partial-onset seizures (NDA 22-254)**

The goal of these studies was to evaluate the use of LCM intravenous infusion for the temporary replacement of the oral dose, in patients who could not tolerate it (such as those patents undergoing surgery). SP616 was a 2-day randomized, double blind study comparing the LCM IV versus oral table formulations (there was no comparison to placebo alone). SP757, was open-label sequential-design study, involving LCM 100 to 400 mg bid infused over 10, 15 or 30 minutes. There were no naïve patients exposed to the IV infusion. All patients in the phase 2/3 studies had been participants in prior oral tablet studies. Table 4 presents phase 2/3 studies with the IV infusion formulation for the epilepsy indication.

Table 4. Phase 2/3 clinical studies with IV infusion Lacosamide for the epilepsy indication

Trial/ country	Design/ duration	Population	Treatment	
SP616 US and Lithuania	Multi-center, DB, double-dummy, randomized. Extension to SP615.	42% male Age 19-67 Cohort A & Cohort B	IV placebo + LCM oral N=30	IV LCM + placebo tablets N=30
SP757 US and non-US	Open label (no placebo)	51% male Age 18-66	100-400 mg bid/IV N=40, 30 min infusion; N=100, infusion 15 min, N=20, infusion 10 min	
Total			**199***	

DB= double-blind. OL= open label. Bid= twice a day. IV= intravenous. Patients in the phase 2/3 IV studies have already been exposed to the oral formulation. * As per the sponsor's table in page 46 of the Clinical Overview.

Additional information on the studies with IV LCM is in Appendix 2.

- **Phase 1 studies**

Phase 1 studies evaluated the safety, tolerability, PK and bioavailability of LCM in healthy volunteers (except for those in subjects with renal or hepatic impairment). A summary of Phase 1 study design/characteristics is presented in Table 5.

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Table 5. Phase 1 studies with LCM

Study	Description (n, gender)
SP657	OL, R, 2-way, crossover 200 mg oral tablet — (n=16, M) b(4)
SP645	OL, R, SD, 2-way crossover (n=24).
SP600	OL, R, SD, 2-way crossover (n=24, M)
SP835	DB, R, PC, SD oral ascending (n=27, M)
SP587	OL, single ascending oral dose (n=16, M)
SP836	DB, R, PC, 7-day oral ascending (n=21, M)
SP588	DB, R, PC, Multiple dose (16 days), oral **capsule** ascending dose (n=33, M) N=24 LCM/9 Placebo. Dose 300 or 500 mg once or twice daily.
SP620	DB, PC, single and multiple (7-day) oral (n=48 M &F), 15 elderly M(11 LCM/4 PL); 16 elderly F (12 LCM/4 Pl, 16 young M (12 LCM/4 Pl).
SP661	DB, R, PC, multiple oral 200 mg in male of different ethnicity. (n=48 M)
SP641	OL, sequential, SD in subjects with renal impairment (n=32, M&F)
SP642	OL, 100mg BID x 4.5 days in subjects with hepatic impairment (12, M& 4F)
SP644	DB, PC, R crossover, digoxin interaction (23, M)
SP660	OL, single and multiple dose, interaction with metformin (M)
SP601	OL, R, multiple dose crossover, valproic acid interaction (n=16 M)
SP602	OL, multiple dose crossover, valproic acid interaction (n=16 M)
SP603	OL, multiple dose, carbamazepine interaction (20M)
SP618	OL, multiple dose, carbamazepine (CBZ) interaction (n=20 M)
SP863	OL multiple dose, omeprazole interaction (36 M)
SP599	OL, oral capsule, Mycrogynon® interaction (40 F)
SP903	DB, R, single site, SD crossover, oral tablet evaluating abuse potential (n=76 M&F)
SP640	DB, single site, R, PC. Thorough QTc (M&F). LCM400 (n=60), LCM 800 (n=71), placebo (N=62), moxif (n=54)
SP619	OL, R, SD, oral & IV (n=10, M)
SP658	OL, R,SD, 3-way cross., oral tablet or IV 200mg over 30 or 60 min (n=22, M)
SP834	DB, R, PC, single IV ascending 50-300 mg (n=28M, 26LCM/4 Placebo)
SP643	OL, R, 2-way crossover (CYP2c19) (n=12) oral & IV infusion

OL= open label. R= Randomized. PC= placebo-controlled. SD= single dose, F= female, M=male. BID= twice a day. Source: Table 1, ISS and individual datasets.

Of the 25 studies, 6 were single-dose and 19 were single and multiple-dose studies. Most of them involved the oral tablet; — one included the oral capsule and four included the IV formulation. Twenty of the 25 studies involved only male subjects. Approximately 140 out of the 644 subjects (22%) were female. The phase 1 development program was entirely conducted outside the US, except for the study SP640, the Thorough QTc study, which was conducted in the US. b(4)

COMMENT: The race distribution in the US is different than in Europe/Australia. Caucasian subjects represented 99% of the EP S2 pool in the Europe/Australian studies, as compared to 85% of patients in the US. This under-representation of non-Caucasian subjects does not appear to be a problem, as the main enzyme involved in LCM metabolism is 2C19. The prevalence of 2C19 poor metabolizers is similar for Whites and Black and somewhat greater in Asians. However, as per discussion with the Clinical pharmacology reviewers, the PK of the parent was not different in the Poor and Extensive metabolizers. The metabolite was 80%

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higher in the EMs, although the metabolite exposure is only 10% of the parent exposure in plasma. These differences are not likely to be clinically relevant and would cover any racial differences observed.

5 CLINICAL PHARMACOLOGY

5.1 Clinical Pharmacology studies

Following oral administration, lacosamide is absorbed with a Tmax of approximately 0.5 to 4 hours after dosing. The elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of repeated administration (twice daily). Pharmacokinetics of lacosamide is dose proportional at the therapeutic doses. Food does not affect lacosamide PK. Absolute bioavailability of lacosamide was determined to be ~100%.

—————————————————. The 30 and 60 minute IV infusions were bioequivalent to the oral tablets, but the 15 minute infusion failed bioequivalence criteria in terms of Cmax, showing a 20% increase in Cmax compared to the oral tablets.

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LCM is mainly metabolized by CYP2C19 to O-desmethyl LCM (also called SPM 12809). O-desmethyl LCM amounts to approximately 10% of the plasma concentration of the parent compound and has no known pharmacological activity.

A study of the effect of LCM in subjects with moderate hepatic impairment found a 50-60% higher exposure of LCM and lower concentrations of the major metabolite in these patients. LCM and its major metabolite are primarily cleared renally. A study of the effect of LCM in subjects with renal impairment found a 60% higher exposure of LCM in these subjects.

Clinical Pharmacology findings are discussed in detail in the reviews done by the Clinical Pharmacology reviewers.

Additionally, the QT team conducted an analysis of SP640 (the QT study). The following is an excerpt from the QT team's overall summary of findings:

> In this randomized, positive- and placebo-controlled, parallel study, 247 healthy subjects were administered multiple oral doses of lacosamide 400 mg/day, lacosamide 800 mg/day, moxifloxacin 400 mg/day or placebo. The supratherapeutic dose chosen for this study is only 33% higher than the highest anticipated therapeutic dose 600 mg/day. The subject exposures in this study may not cover the increases in lacosamide concentrations due to moderate to severe hepatic and renal impairment for the ——— dose of 600 mg/day, although it would for a maximum dose of 400 mg/day.
>
> At both lacosamide doses, the upper limits of the two-sided 90% CI for the difference between time-matched, baseline-adjusted QTcI in least squares means between the drug and placebo were less than 10 msec, the threshold of regulatory concern identified in the ICH E14 guideline. In fact, the study suggests lacosamide shortens the QTc. At Tmax on day 6, the mean change after administration of lacosamide 400 mg/day in QTcI from baseline compared to placebo was –9.4 with an upper one-sided 95% CI of –4.2; for 800 mg/day the values were –7.4 and –3.3,

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respectively. Shortening of the ΔΔQTcI intervals were also observed on day 1 and day 3. The ICH E14 guideline makes no recommendation for the development or labeling of products which shorten the QT interval because adequate data upon which to base a recommendation do not currently exist.

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

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

In summary, there is no evidence of a QTc prolongation effect of LCM over placebo. If something, there is suggestion for a QTc shortening.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy review for of LCM as adjunctive therapy in subjects with partial-onset seizures is being done by Dr. Hershkowitz (DNP); the efficacy review for the treatment of Diabetic Neuropathic Pain is being done by Dr. Pokrovnichka (DAARP).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Adverse events (AEs) in this application were coded using MedDRA 9.1. Events were included for analyses if they occurred up to 30 days following the last dose of trial medication. For the ongoing trials, the cutoff date for analysis of the original submission was October 2006. The cutoff date for analysis of the 120-day Safety Update was June 12, 2007. The safety analyses of the Pool EP S2 presented in the SUR are consistent with those in the original submission. There is no updated information for the S1 Pools. Unless noted otherwise, summary tables and analyses in my safety review are based on data submitted in the original submission.

This review will follow the FDA Review Template for the phase 2/3 studies in partial-onset epilepsy (with the oral tablet, oral capsule [studies 586 and 598] and the IV infusion) followed by the phase 1 studies.

7.1.1 Deaths

There were a total of 9 deaths across 1327 subjects in the Phase 2/3 LCM partial-onset seizure trials and 15 deaths across 1566 subjects in the Phase 2/3 LCM neuropathic pain trials.

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Of the 9 deaths in the epilepsy population, 4 were considered possible sudden unexpected death in epilepsy (SUDEP), 1 was a completed suicide, 1 was a road traffic accident, 1 was due to intracranial hypertension, 1 was a glioblastoma and 1 presented a cerebral hemorrhage thought to be secondary to injury during an epileptic seizure. They occurred in 5 male/4 female, ages 25 to 62, 8 Caucasian/1 African American. Eight of the nine occurred during open label extensions. None were on placebo. None of the deaths were attributed by the investigator to be LCM-related deaths. Review of the narratives and CRFs for these cases do not suggest drug-related toxicity.

There were no deaths in the Phase 1 studies, 2/3 trials with the IV infusion or oral capsule.

A summary of the cases is presented in Table 6.

Table 6. Summary of Deaths in Epilepsy studies

	Paient ID	Age/ gender	LCM Dose (mg/d)	Relative day on LCM Rx	Cause of death	Relevant past medical history/comments
1	615/667013303 (Subject 10062 in SP615)	54 F	600	1130	Asphyxia/ seizure related *(Sponsor identified as potential SUDEP)*	Randomized to LCM 600 mg/day, started LCM on 4/22/03; entered OL extension on 9/11/03. She was found dead at home on — Autopsy states cause was seizure. At the time of the AE she had been at 600 mg/day dose for 592 days. AEs throughout the study: decreased memory, ataxia, dizziness and nausea. Last available visit on 1/10/06 showed normal ECG & labs. She reported that she had fewer seizures but her headaches were coming back. Concomitant meds: clonazepam, valproic acid, APAP, ketoconazole & clotrimazole cream, naproxen and amitriptyline (for last four months for headaches and arm pain).
2	615/667014301 (Subject 11976 in SP615)	39 M	500	1185	R frontal Glioblastoma Multiforme	Hx of bilateral blindness and of brain mass 8 years prior to entry. Concomitant medications included levetiracetam, topiramate, APAP, and ranitidine. On rel day 1073 (day 777 at 500 mg/day) he developed confusional state requiring hospitalization. Diagnosis of tumor recurrence was made. He was treated with dexamethasone and no chemotherapy. Last ECG & lab evaluations 3 months prior to death were normal.
3	615/667016105 (Subject 11428 in SP615)	30 M	200	490	Status epilepticus (Sponsor identified as potential SUDEP)	The subject experienced status epilepticus of severe intensity on — At the time of the AE the subject he had been on 200 mg/d for 379 days. He was having one seizure every 2-3 months. Concomitant medications at the onset of the serious AE included gabapentin and topiramate. ECG & Labs at last available visit (4/5/04) were normal. The autopsy report indicated that the cause was seizure-induced respiratory and circ. insufficiency.
4	615/667017720 (Subject 11614 in SP615)	28 M	600	726	Road traffic accident	The subject began LCM 400 mg/day treatment group on 10/09/03 and entered OL phase on 2/23/04. He was walking through a crosswalk and was run over by a tram on — . He died of internal bleeding. Prior to the fatal traffic accident, the subject reported moderate balance disorder (ataxia) from 9/04 to 1/05 months prior) and unsteadiness from March to May 05, while taking LCM 700 mg/day. The events improved with dose reduction. Concomitant medications included phenytoin. At the time of death, the subject was taking lacosamide 600mg/day and had been at this dose level for 136 days. Last evaluation 2 weeks prior to death showed normal ECG and labs.

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	Paient ID	Age/ gender	LCM Dose (mg/d)	Relative day on LCM Rx	Cause of death	Relevant past medical history/comments
5	667/667012803 (during DB)	63 M	200	120	Completed suicide/gunshot	Randomized to LCM 200mg/day on 05 Jun 2002. It cannot be confirmed that this subject was taking trial medication during the 3 weeks preceding the death. He had a history of depression, but was stable and not taking any antidepressants. He reported an AE of depression upon learning that his wife was diagnosed with cancer on 9/11/02. As per disposition dataset, fist dose LCM started 7 04 02, last dose recorded 9 11 02 (68 days of treatment). On — the subject committed suicide by self inflicted gunshot wound. b(6)
6	756/754012317	28 F	400	275	Cardiorespiratory arrest (Sponsor identified as potential SUDEP)	Randomized to LCM 400 mg/day, started on Dec 14, 2005. Completed double blind and entered the OL phase on 5/3/06. On — she died of cardiorespiratory arrest. Last available visit in CRF was 8/24/06. She was having 1-2 seizures a month (the last seizure was reported to be 8/19/06). There were no abnormal laboratory values, blood pressure or heart rates noted in the database that appear to indicate death was imminent or likely. She was taking concomitant phenytoin and topiramate. There were no cardiac-related concomitant medications. AE included diplopia, GE reflux and depression, for which the dose was not changed. Zoloft 50 mg/day and omeprazole 20 mg/day were started on 6/2/06. Diplopia and reflux recovered but depression was ongoing at the time of death. Of note, she lost 11 Lbs over 4 months (170 Lbs at entry to OL, 159 Lbs at visit 4). No other details regarding this event are available other than the notation that the subject was at home when the cardiac arrest occurred. She did not have an autopsy. b(6)
7	756/754017409	30 M	400	90	Convulsion/ sequelae of seizure disorder (Sponsor identified as Potential SUDEP)	Patient received placebo in base study. Started Lacosamide 300 mg/day on 4/24/06. At time of the AE of convulsion on —, he had been on Lacosamide 400 mg/day for 68 days. He was found dead at home, the same day that he had the seizure. He had reported AE of dizziness over the prior 2 months. Last available visit 6/19/06 showed normal ECG and electrolytes. The only seizure recorded in the dataset was on 6/15/06. No autopsy was performed and no other details regarding the death are available. Initial cause of death was recorded as Sudden death cause unknown, later changed to "sequelae of seizure disorder". Concomitant med at entry was gabapentin; it appears that it was stopped on 5/22/06. b(6)

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	Paient ID	Age/ gender	LCM Dose (mg/d)	Relative day on LCM Rx	Cause of death	Relevant past medical history/comments
8	774/755122105	39 F	600	130	Intracranial hypertension, status epilepticus, subarachnoid hemorrhage	Received placebo in base study. Started LCM 200 Aug 13 through Dec 21, 2005. Prior to the AE she was hospitalized for in-video EEG. Doses of other AEDs were reduced x 9 days. Electrodes removed on Dec 7. She had fever and was treated with antibiotics on Dec 8. On Dec 13 had status epilepticus & SAH. At time of death (— she had been on LCM 600 x 39 days.
9	774/114111*	40 F	200	268	Intracerebral hemorrhage	She entered the double-blind trial SP755 and began dosing with Lacosamide 400mg/day on 18 May 2005. She completed the 12-Week of treatment, entered the open-label SP774 trial, and began lacosamide 200mg/day on 22 Sep 2005. At the time of the serious adverse event (AE), the subject was taking lacosamide 200mg/day and had been at this level for 16 days after having taken lacosamide 300mg/day for 252 days. On — the subject experienced a severe cerebral haemorrhage and was admitted to hospital in a coma. Computed tomography (CT) revealed an intracerebral hemorrhage of the left temporal hemisphere which was regarded as traumatic due to injury during an epileptic seizure. The hemorrhage was evacuated on the same day. A follow up CT scan performed on — revealed a subdural hematoma on the contralateral left side. The patient underwent surgery on — but remained in a coma. She was discharged from hospital and admitted to a hospice on — where she died a few days later. Concomitant medications at the onset of the SAE included topomax 300mg/day. The cerebral haemorrhage was reported as a serious (category results in death). The investigator considered the event unlikely to be related to the trial medication and highly probably related to the subject's epilepsy.

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ID is the subject number in the primary (i.e., double blind) trial. In some cases the subject number in the primary trial and the trial in which the fatal outcome occurred is different (the later is in parenthesis). Dose refers to the dose the subject was on at the time of the AE leading to death. Relative day of treatment refers to time on LCM. * Case submitted with the 120-day safety update report.

- Comment on cases of sudden unexpected death in epilepsy (SUDEP)

Sudden unexpected death in epilepsy (SUDEP) is one of the most common epilepsy-related causes of death. SUDEP has been defined as the sudden unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal toxicologic or anatomic cause of death.[2] The risk of SUDEP has been reported to be less than 1:1000 per year in mild idiopathic epilepsy and up to 1:200 per year in severe refractory epilepsy.[3] A recent or ongoing seizure is identified in approximately 90% of cases of SUDEP, however, 10% are unwitnessed and in 10% of these cases there is no evidence of seizure activity.[2] Central or obstructive apnea and cardiac arrhythmia are the most probable pathophysiological mechanisms, but no definite mechanism has yet been identified. In this application, the sponsor used a slightly different definition of SUDEP that does not include post-mortem examination (Leestma et. al, 1997).

In this application, one of the potential cases of SUDEP occurred during a witnessed status epilepticus (which would be excluded as SUDEP by Brown's definition) and three were unwitnessed. Of these, one occurred in patient who had had a witnessed seizure earlier in the day, one had an autopsy that attributed the cause of death to asphyxia/seizure, and the other occurred in a patient who was found dead (diagnosis of cardiorespiratory arrest) and did not have an autopsy (ID# 756/754012317).

> *Additional information submitted by the sponsor regarding patient 756/754012317at the FDA request did not add to what was already in the original CRF except for some recordings of sinus arrhythmia and ectopic atrial rhythm during the placebo treatment. I agree that this is a potential case of SUDEP.*

Of note, the lamotrigine (Lamictal®) label reads as follows:

> PRECAUTIONS
> **Use in Patients With Epilepsy:**
> ***"Sudden Unexplained Death in Epilepsy (SUDEP):*** During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for LAMICTAL, to 0.005 for

[2] Nashef and Brown. Epilepsy and sudden death. Lancet 1996;348:1324–5.
[3] Aurlien et al. Lamotrigine in idiopathic epilepsy – increased risk of cardiac death? Acta Neurol Scand 2007: 115: 199–203.

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> patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided.
>
> Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving LAMICTAL and those receiving another antiepileptic drug that underwent clinical testing in a similar population at about the same time. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect."

Overall, 1327 subjects with partial-onset seizures received LCM during Phase 2 or Phase 3 trials in this development program, representing 1803 person-years of exposure (EP Pool S2). Based on four events, the sponsor's estimated average rate of SUDEP in this application is 2.22 cases per 1000 PYRs or 0.002 per patient-year.[4] This rate is within the range of what is expected for this population with chronic, refractory seizures.

- Comment on suicidality

The rate of suicide among people with epilepsy is greater than the general population. Because of the current concern that antiepileptic drugs may be associated with an increase risk of suicidality, the FDA requested a specific analysis of suicidality in patients taking LCM. This issue is discussed under section 7.1.3.5. of this review ("Other events of interest": suicidality).

- Deaths in the Neuropathic Pain population

There were 15 deaths among the DPN population, all of them in patients receiving LCM. Four of them occurred during the controlled phase of the studies. Of the 15, 8 were cardiac-related (ventricular fibrillation, myocardial infarction, heart failure (n=2), myocarditis, cardiac arrest (n=2) and sudden death [found dead at home, possible MI]); one was a completed suicide (occurred 72 days after last dose of LCM); one was in a patient with head trauma/subdural hematoma/cardiopulmonary failure and 5 were cancer-related (ovarian, pancreatic, bronchial, colon and leukemia). The cardiac deaths occurred in patients with previous cardiovascular history, including diabetes mellitus plus hypertension, coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Three of them occurred during the controlled phase of the studies (3/1023, 0.3% on LCM vs. 0/291, 0% on placebo).

As per Dr. Pokrovnichka's review of the narratives, the relationship to LCM can not be ruled out in two of the cases (subjects # 74213002, a 45 year-old male with diabetes and coronary artery disease (CAD) who was found in ventricular fibrillation on Day 9, while on LCM 200 mg/day, and # 768108217, a 49 year old male with diabetes, hypertension and ischemic cardiomyopathy who had a cardiac arrest on Day 40, while on LCM 600 mg/day). Additionally, a 67 year old

[4] At the time of the SUR, the exposure was 2088 PYRs, therefore the rate is still the same, 4/2088= 1.9 per 1000 PYRs or 0.002 per patient-year.

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patient with diabetes, CAD and hypertension (745/174401) experienced a fall down a flight of stairs with coma, skull fracture and subdural hematoma which resulted in death while on LCM 300. No ECG data or information about associated symptoms are available from the time of the event, therefore it is not known whether the fall was due to CNS or CV cardiovascular AEs.

One death occurred in patient 2 ½ months after completion of LCM treatment. Patient 830/111201 was a 39 year old patient with neuropathic pain who presented sinus tachycardia (110 bpm) with normal ECG intervals on 7/27/05 during the titration phase, at the dose of LCM 600 mg daily. The event was reported to resolve without changes in LCM dosing. The last dose of LCM (400 mg daily) was reported to be on 8/18/06. On [redacted] the subject died due to "myocarditis (toxic damage to the myocardium) and alcoholic intoxication and toxic damage of the liver." The investigator noted that the subject had no history of alcohol abuse and that the date of onset of the toxic damage of the liver is unknown. No further information regarding this diagnosis is available.

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> *This case is of concern because the date of onset of the myocarditis and toxic hepatitis are unknown. Moreover, the toxic hepatitis is said to be alcoholic, but at the same time the investigator states that the subject did not have a history of alcohol abuse. This case could be consistent with a multi-organ hypersensitivity reaction. Additional information has been requested and is pending at the time of this review.*

For additional details on the deaths in the neuropathic pain population the reader is referred to Dr. Pokrovnichka's review.

The overall mortality rate in the LCM studies, including all formulations and indications is 0.6% (24/4012). The mortality rate in EP S1 + DPN S1 (placebo-controlled studies of at least 12 weeks duration) was 0.3% (5/1967) among patients randomized to LCM and 0% on placebo (0/655). Of the 5 deaths that occurred in the controlled studies, 3 were cardiac-related. Given the different exposure of LCM and placebo treatment groups definitive conclusions can not be drawn regarding whether LCM increases the risk of cardiac-related death.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) are defined as those that result in death, are life-threatening, require hospitalization or prolonged hospitalization, result in persistent or significant disability/incapacity or congenital anomaly or birth defect or are considered to be an important medical event.

- **Placebo-controlled epilepsy studies (EP Pool S1)**

In placebo-controlled trials (EP Pool S1), 6.5% of all LCM-treated subjects reported a treatment emergent serious adverse event (SAE) compared to 3.8% of subjects on placebo.

The most frequently reported TE SAEs in this population were in the Nervous System disorders System Organ Class (SOC) (2.1% for LCM and 1.6% for placebo-treated patients), with the most frequent preferred term being convulsion for both LCM and placebo-treated patients (0.8% each).

The next most frequent TE SAEs were in the Psychiatric disorders SOC (0.7% for LCM and 0 for placebo-treated patients, respectively) and GI disorders systems (0.6% for LCM and 0.3% for placebo-treated patients, respectively). Analyses of SAEs did not show a clear dose response among LCM treated patients, however, the size of the database is relatively small to detect differences in SAEs by treatment dose. Moreover, the total number of patients randomized to LCM 600 is half of those randomized to LCM 400 and given a 40% dropout rate in the LCM 600 group, the exposure to LCM 600 is substantially smaller than to the LCM 400 group. Additionally, by design patients underwent dose titration up to the target (randomization) dose, therefore a patient may have presented the event at a dose lower than the randomization dose and be counted under the randomization dose group. A summary table of serious adverse events by SOC in the EP Pool S1 by randomized dose during the treatment phase (titration and maintenance) is presented in Table 7.

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Table 7. Serious treatment emergent AE in placebo-controlled studies in subjects with partial onset seizures (Pool EP S1) during the treatment phase, by randomization dose

MedDRA System Organ Class Patients with at least one event	Placebo (N=364) n (%)	LCM (mg/day) 200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Any system organ class	14 (3.8)	21 (7.8)	34 (7.2)	6(3.0)	61 (6.5)
Blood and lymphatic system disorders	0	0	1 (0.2)	0	1 (0.1)
Cardiac disorders	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Congenital, familial and genetic disorders	0	0	0	1 (0.5)	0
Ear and labyrinth disorders	0	0	2 (0.4)	0	2 (0.2)
Eye disorders	0	0	0	1 (0.5)	1 (0.2)
Gastrointestinal disorders	1 (0.3)	1 (0.4)	4 (0.9)	0	6 (0.6)
General disorders and admin site condit.	0	1 (0.4)	2 (0.4)	0	3 (0.3)
Hepatobiliary disorders	0	0	1 (0.2)	0	1 (0.1)
Infections and infestations	1 (0.3)	0	3 (0.6)	2 (1.0)	5 (0.5)
Injury, poisoning and procedural complic.	0	2 (0.7)	3 (0.6)	0	5 (0.5)
Investigations	1 (0.3)	3 (1.1)	2 (0.4)	0	5 (0.5)
Metabolism and nutrition disorders	1 (0.3)	1 (0.4)	1 (0.2)	0	2 (0.2)
Musculoskeletal and connective tissue dis.	0	1 (0.4)	0	1	2 (0.2)
Neoplasms benign, malignant and unspec.	1 (0.3)	3 (1.2)	0	0	3 (0.3)
Nervous system disorder	6 (1.6)	6 (2.2)	11 (2.3)	3 (1.5)	20 (2.1)
Pregnancy, puerperium and perinatal cond.	0	0	1 (0.2)	0	1 (0.1)
Psychiatric disorders	0	1 (0.4)	6 (1.2)	0	7 (0.7)
Renal and urinary disorders	0	1 (0.4)	1 (0.2)	0	2 (0.2)
Reproductive system and breast disorders	1 (0.3)	1 (0.4)	1 (0.2)	0	1 (0.1)
Respiratory, thoracic and mediastinal dis.	1 (0.3)	1 (0.4)	1 (0	0	2 (0.2)

Note: n = Number of subjects who reported at least one event during the phase. % = Percent with respect to the number of subjects in Pool S1. Treatment phase Includes titration and maintenance phase. Source Table EP 6.25.1, Clinical Summary of Safety.

The overall rate of TE SAE is higher with LCM as compared to placebo (6.5% and 3.8%, respectively). There does not seem to be a dose-response relationship. At the FDA request, TE SAE in S1 by dose at time of onset of event was submitted by the sponsor on 2/19/08. The rate of TE SAE by dose at time of onset was as follows: Placebo: 2.7%,, LCM 100: 1.2%, LCM 200: 2%, LCM 300: 0.3%), LCM 400:3.5%, LCM 500: 1.2%, LCM 600: 1.9%.

The interpretation of the information is complicated by the smaller exposure to LCM at doses >400 mg/day.

Treatment emergent SAEs in the Nervous system disorders SOC by randomization dose are presented in Tables 8 and 9.

Table 8. TE Serious AE for the Nervous system disorder SOC, Pool EP S1 during treatment phase by randomized dose

MedDRA System/Organ Class Patients with at least one event	Placebo (N=364) n (%)	LCM (mg/day) 200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Nervous system disorders					
Any	6 (1.6)	6 (2.2)	11 (2.3)	4 (2.0)	20 (2.1)
Convulsions	3 (0.8)	3 (1.1)	5 (1.1)	0	8 (0.8)
Dizziness	0	0	0	3 (1.5)	3 (0.3)
Nystagmus	0	0	0	2 (1.0)	2 (0.2)
Grand mal convulsion	1 (0.3)	0	2 (0.4)	0	2 (0.2)
Epilepsy	1 (0.3)	2 (0.7)	0	0	2 (0.2)
Coordination abnormal	0	0	0	1 (0.5)	1 (0.1)
Tremor	0	0	0	1 (0.5)	1 (0.1)
Hemiparesis	0	0	1 (0.2)	0	1 (0.1)
Loss of consciousness	0	0	1 (0.2)	0	1 (0.1)
Nervous system disorder	0	0	1 (0.2)	0	1 (0.1)
Status epilepticus	0	0	1 (0.2)	0	1 (0.1)
Somnolence	0	1 (0.4)	0	0	1 (0.1)
Complex partial seizures	1 (0.3)	0	0	0	0
Migraine	1 (0.3)	0	0	0	0
Partial seizures	1 (0.3)	0	0	0	0

LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=system organ class. Data source: Sponsor's table. ISS EP 6.25.1.

The most common serious AE in the Nervous System disorders SOC was "convulsions" followed by dizziness and nystagmus. The listing of subjects who developed treatment emergent serious adverse events (TE SAEs) during the titration or maintenance phase is presented in the following table.

Note that several tables in this review will have a similar heading, including ID (patient identification), PT (MedDRA preferred term), AE term (investigator reported term), Action (action taken with the drug), Outcome (whether the event resolved [R] or did not resolve [No R], the Rel. st day (relative day of study) and AE dose (dose at onset of the AE).

Table 9. Lacosamide. Treatment emergent Serious Adverse Events during the treatment phase in EP S1

ID	PT	AE term	Action	Out come	Rel st day	AE DOSE
Placebo						
667012101	Convulsion	Increased seizure activity following oral surgery	Dose not changed	R	125 (M)	0
667015009	Grand mal convulsion	Grand mal during visit	Withdrawn	R	100 (M)	0
755100804	Migraine	Migranous headache	Dose not changed	R	18 (T)	0
755104410	Epilepsy	Epileptic seizure	Dose not changed	R	4 (T)	0
755110109	Complex partial seizures	Series of complex-focal seizures	Withdrawn	R	13 (T)	0
755100705	Partial seizures	Prolonged focal seizure	Dose not change	R	51 (M)	0
LCM 200						
667011910	Convulsion	Increased number of seizures	Withdrawn	R	1 (T)	0
667012304	Convulsion	Hospitalization for seizures after d/c for increased transamin	Withdrawn	R	1 (T)	100
755100110	Convulsion	Increase in seizures	Dose not changed	R	7 (T)	0
755100405	Somnolence	Drowsiness	Dose not changed	R	46 (M)	100
	Somnolence	Drowsiness (worsening)	*Dose reduced*	R	27 (T)	200
755104110	Epilepsy	Epileptic seizure	Dose not changed	R	108 (M)	200
755124611	Epilepsy	Epileptic seizures.	Dose not changed	R	8 (T)	0
LCM 400						
667010404	Convulsion	Increase in frequency of seizures	Dose not changed	R	5 (T)	0
	Convulsion	Seizures	Withdrawn	R	99 (M)	400
667011801	Loss of consciousness	Loss of consciousness	Dose not changed	R	43 (T)	400
667011906	Convulsion	Hospitalization for prolonged seizure (15 mins)	Dose not changed	R	66 (M)	400
754010107	Status epilepticus	Status epilepticus	Withdrawn	R	31 (T)	400
754010714	Hemiparesis	Right hemiparesis	Dose not changed	R	10 (T)	200
754012512	Convulsion	Seizure lead to hospitalization	Withdrawn	R	1 (T)	200
754013604	Convulsion	Increased seizure frequency requiring hospitalization	Withdrawn	R	1 (T)	100
754016013	Nervous system disorder	Worsening of alien hand syndrome	Withdrawn	R	15 (T)	200
755104307	Grand mal convulsion	Hospitalized due to generaliz tonic clonic seizures	Withdrawn	R	7 (T)	100
755108202	Convulsion	Hospitalisation for 3 seizures	Dose not changed	R	28 (T)	400
	Status	Hospitalisation for status	Withdrawn	R	123 (M)	0

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ID	PT	AE term	Action	Out come	Rel st day	AE DOSE
	epilepticus	epilepticus				
755110204	Grand mal convulsion	2 grand mal seizures	Dose not changed	R	24 (T)	400
	Grand mal convulsion	Grandmal seizure	Dose not changed	R	73 (M)	400
LCM 600						
667010202	Coordination abnormal	Ataxia-broad based ataxia during gait walking	Withdrawn	Ongoing	3 (T)	100
	Dizziness	Dizziness	Withdrawn	Ongoing	3 (T)	100
	Tremor	Tremor-at rest and increased with finger nose finger	Withdrawn	Ongoing	3 (T)	100
667016104	Dizziness & nystagmus	Dizziness	Withdrawn	R	41 (T)	600
667017401	Dizziness	Dizziness	Withdrawn	R	35 (T)	500
667010202	Nystagmus	Nystagmus	Withdrawn	R	8 (T)	100

Source. AE Datasets for EP S1 submitted January 2008. PT=preferred term. AE term=investigator term. R= recovered/resolved. (M)= maintenance. (T) titration. Rel day= relative day of onset. AE dose= dose taken at time of onset of the AE.

Dizziness, ataxia and nystagmus, are known to occur with other AEDs and likely to be related to LCM. One case of syncope (loss of consciousness) was reported as a serious AE in the Nervous system disorders SOC. This AE is discussed later under section 7.1.3.2 (Syncope) of this review.

In addition to convulsions, other preferred terms (PT) were used to code seizures (grand mal convulsion, epilepsy, partial seizures and status epilepticus). The rate of treatment emergent serious convulsion (and related terms) during EP S1 are presented in Table 10.

Table 10. TE serious convulsion and related terms in EP S1

MedDRA PT related to seizure activity	Placebo (N=364) n (%)	LCM (mg/day)			
		200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Any	5 (1.4)	5 (1.9)	8 (1.7)	0	13 (1.4)
Convulsion/grand mal conv.	2	3	7	0	10
Epilepsy	1	2	1	0	3
Partial seizures	2	0	0	0	0
Status epilepticus	0	0	2	0	2

It is very difficult to establish causality for seizures in this population. It is unclear what the criterion was for some investigators to determine that a case of seizure represented an adverse event or represented lack of efficacy. See additional discussion about seizures under Dropouts due to AEs.

Overall, the rate of serious convulsion and related terms was similar for LCM and placebo. A similar number of events occurred in the titration and maintenance phases of LCM treatment (n= 8 and 7, respectively). Of note, one patient (ID# 66712304) presented seizures during maintenance after LCM discontinuation due to increased transaminases (this case is discussed later under AE of interest). In addition to this seizure short after stopping LCM, three patients presented seizure-related AE terms during the tapering phase (See table 11). Therefore there is some evidence that, consistent with other antiepileptic drugs, drug withdrawal seizures may occur if LCM dose is stopped or decreased.

Table 11. Serious AE of seizure during tapering phase

Pt ID	PT	AE term	Action	Out come	Rel st day	AE Dose
754018904	Convulsion	Seizure	Dose not changed	R	48	200
755104409	Epilepsy	Epileptic seizure	Dose not changed	R	83	0
755108202	Status epilepticus	Hospitalization for status epilepticus	Withdrawn	R	123	0

Source. AE Datasets for EP S1 submitted January 2008. PT=preferred term. AE term=investigator term. R= recovered/resolved. (M)= maintenance. (T) titration. Rel day= relative day of onset. AE dose= dose taken at time of onset of the AE.

- Serious adverse events in the Psychiatric SOC

Seven subjects had serious adverse reactions in the Psychiatric disorders SOC, including psychosis and hallucination in EP S1 (see table below). No such events were observed in the placebo group.

Table 12. Treatment emergent SAE in the Psychiatric disorders SOC during the treatment phase, in EP pool S1, by randomization dose

MedDRA System/Organ Class Patients with at least one event	Placebo (N=364) n (%)	LCM (mg/day) 200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Psychiatric disorders					
Any	0	1 (0.4)	6 (1.3)	0	7 (0.7)
Psychotic disorder	0	0	2 (0.4)	0	2 (0.2)
Depression suicidal	0	0	1 (0.2)	0	1 (0.1)
Epileptic psychosis	0	0	1 (0.2)	0	1 (0.1)
Hallucination, auditory	0	0	1 (0.2)	0	1 (0.1)
Hallucination, visual	0	0	1 (0.2)	0	1 (0.1)
Suicide attempt	0	0	1 (0.2)	0	1 (0.1)
Insomnia	0	1 (0.4)	0	0	0

LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=system organ class. Data source: Sponsor's table. ISS EP 6.25.1.

The listing of patients with serious TEAE in the Psychiatric disorders SOC is shown below.

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Table 13. Treatment Emergent Serious AE, Psychiatric disorders SOC, EP S1, by HLT.

ID	Age, Gender	TrGroup	PT	AE term	Action	Outcome	Rel day	AE Dose
Perception disturbances HLT								
754011216	27, M	LCM 400	Hallucinations	Auditory & visual hallucinations[1]	Dose not changed	R	57	400
Psychotic disorders NEC HLT								
755100704	36, F	LCM 400	Epileptic psychosis	Post-ictal psychosis causing hospitalization	Dose not changed	R	73	300
755106305	24, F	LCM 400	Psychotic disorder	Hospitalization due to psychotic thoughts	Dose not changed	R	90	400
755124609	52, M	LCM 400	Psychotic disorder	Psychosis with abnormal beliefs	WITHDRAWN	No R	31	400
Suicidal and self injurious behavior HLT								
667012803	62, M	LCM 200	Completed suicide	Suicide by self-inflicted gunshot wound	WITHDRAWN	No R	21	200
754012512	52, M	LCM 200	Suicide attempt	Cut his wrist (suicide attempt)	WITHDRAWN	R	2	200
Disturbances in initiating and maintaining sleep HLT								
755106307	19, F	LCM 200	Insomnia	Insomnia	Dose no changed	R	128	200

R= recovered, resolved. No R= not recovered. Source: AE datasets EP Pool S1 submitted January, 2008.

Patients with epilepsy are at risk of developing a variety of psychiatric problems, including depression, anxiety, and psychosis. This risk varies considerably depending on many factors, including the etiology, frequency, and severity of seizures and the patient's age and previous history.[5] It is unclear whether LCM may increase the risk of developing psychiatric AEs. The numbers are small but all the serious cases occurred in LCM treated patients.

The narrative of the patient with hallucinations is as follows: b(6)

Subject 11216 was a 28-year-old white male with history of headaches, chronic pain and depression, He was randomized to lacosamide 400mg/day on [redacted]. At the time of the serious adverse events/abuse liability adverse events, the subject was taking lacosamide 400mg/day and had been at this dose level for 34 days (total exposure to trial medication 57 days). On that day, he developed auditory and visual hallucinations and was admitted to the emergency room. A urine drug screen was performed during the hospitalization and was positive for marijuana and amphetamines. The subject was discharged from the hosptial on [redacted]. The final outcome of the event was reported as recovered/resolved. Trial medication was unchanged, remained blinded, and the subject continued in the trial. Concomitant medications at the time of the event included ibuprofen, valproate, levetiracetam, venlafaxine and zonisamide. b(6)

5 Harrison's Principles of Internal Medicine,, 17th Ed. (2008)

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In this case, the AE of hallucination is confounded by a positive screening test for marihuana and amphetamines. The case does not appear to be directly related to LCM use. However other cases of hallucinations were also reported in the LCM program.

The three psychotic disorders are as follows:

- **Subject 100704** was a 37-year-old white female with history of headache,and developmental delay. She was randomized to LCM 400 on 26 May 2005. At the time of the adverse event (AE), the subject was taking LCM 300 and had been at this dose level for 44 days. On ——— , she developed confusion and inappropriate behavior 4 hours after trial medication. The AE was considered mild in intensity and resolved on the same day, but required hospitalization. Trial medication dose was unchanged. Concomitant medications at the onset of the AE included lamotrigine, oxcarbazepine and acetaminophen. The "epileptic psychosis" was reported as a serious AE.

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Comment: the investigator considered the "epileptic psychosis" unlikely to be related to trial medication, and highly probably related to the underlying disease. Psychotic thoughts may occur in patients with epilepsy. There was no mention of previous psychotic thoughts in this patient. The narrative and CRF lack details as to the criterion for determining that this was disease related.

-Subject 106305 was a 24-year-old white female. Her medical history included dysmenorrhea and headache. She was randomized to lacosamide 400mg/day on 30 Mar 2005. At the time of the AE the subject was taking lacosamide 400mg/day and had been at this dose level for 69 days. On 27 Jun 2005, during the dose Maintenance Period, the subject experienced psychotic disorder. As per the investigator, psychotic thoughts appeared to be of organic origin and related to the severe frontotemporal epilepsy. No psychiatric medication was used to treat the subject. The subject experienced several epileptic seizures during the prior weekend. The AE was considered severe and was considered resolved on 02 Jul 2005. Trial medication was unchanged.

Comment: in this case the patient had experienced severe seizures during the prior weekend and had severe frontotemporal epilepsy. The description is consistent with epileptic psychosis but there is no mention of previous episodes of psychosis in this patient. The relationship to LCM is unclear.

- Subject ID# **124609** was a 52-year-old white male with a history of depression, amnesia (30 years prior to study entry), head injury (unknown date), persecutory type delusional disorder (unknown date), panic attack (unknown), and psychotic disorder (unknown date). The subject was randomized to LCM 400 on 01 Jul 2005. At the time of the AE on July 31, 2005, the subject was taking LCM 400 and had been on this dose level for 11 days. The AE was reported as a psychotic disorder (psychosis with abnormal beliefs). The subject behaved strangely, had inappropriate arguments with his wife, and also experienced poor memory. Amnesia, depression, and headaches were all ongoing illnesses. No other information about the symptoms and behavior are available. Trial medication was discontinued (last dose taken on August 25, 2005). Al last follow up (September 15, 2005) the event had not resolved. Concomitant medications at the time of the onset of the AE were lamotrigine, clobazam, mirtazapine and ibuprofen. The investigator considered that the event was highly probably related to trial medication.

This patient had a prior history of delusional disorder and psychotic disorder. There is very limited information about the episode of psychosis that occurred during this trial but the role of LCM can not be ruled out.

There were two suicidality-related cases (one completed suicide and one attempted suicide), one case of hallucinations and 3 psychotic disorders (one of them requiring withdrawal). No serious psychiatric disorders occurred on placebo. Subject # **667012803** was described in Table 6 (deaths). Subject # **754012512** attempted suicide while hospitalized during a seizure. AE causality is difficult to determine in both cases. Patients with epilepsy are at increased risk of suicide. Suicidality is discussed later under in section 7.1.4.4 of this review.

- Serious AEs in the GI disorders SOC

Treatment emergent SAEs in the Gastrointestinal disorders SOC – the third most common SOC category- in EP Pool S1 consisted of one case of abdominal adhesions in the placebo group and nausea, vomiting, abdominal pain, peritonitis, pancreatitis and tooth disorder in the LCM treated group. These cases are listed in Table 14.

Table 14. Treatment emergent SAE in the GI disorders SOC

ID	Age, Gender	PT term	Action	Out come	Rel day	AE Dose
Placebo						
667010638	46, F	Abdominal adhesions	dose not changed	R	77	0
LCM 200						
667015024	45, F	Nausea	withdrawn	R	43	200
667015024	45, M	Vomiting	withdrawn	R	43	200
LCM 400						
667013401	49, M	Loss of teeth[1] (seizure)	dose not changed	No R	102	400
667016208	53, F	Peritonitis	drug interrupted	R	75	400
754010605	37, M	Pancreatitis	withdrawn	R	2	100
754016905	43, F	Abdominal pain	drug interrupted	R	46	400
LCM 600						
667017401	34, F	Nausea	withdrawn	R	35	500
667017401	34, F	Vomiting	withdrawn	R	35	500

[1] Seizure with fall and loss/removal of 7 teeth. Source: AE datasets EP S1 submitted January, 2008.

Nausea and vomiting have been reported in non-clinical studies and phase 1 studies. Review of the narratives of the case of pancreatitis and peritonitis do not suggest that the events were drug related.

- Serious AEs in other SOCs

The next most frequent SOC categories for serious TAES were as follows: Infections and infestations; Injury, poisoning and procedural complications; and Investigations.

Regarding serious infections, there was one case of appendicitis in the placebo group (0.3%) versus 2 cases of appendicitis, one cellulitis, one labyrinthitis, one nasopharyngitis and one sinusitis in the LCM group (0.5%). These are common infections and do not appear to be related to LCM use.

Regarding SAE in the Injury, poisoning and procedural complications it does not seem to be an increased risk for these events in the LCM treated patients as compared to placebo. For the Investigations SOC there were 4 on LCM and 1 on placebo but 2 of these were on placebo at the time of the event. The listing of these cases is presented in Table 15.

Table 15. Treatement emergent SAEs in the Injury, Poisoning & procedural complications and Investigations SOCs, in EP S1.

ID	Age, Gender	Tr group	PT term	Action	Outcome	Rel st day	AE Dose
Injury, poisoning and procedural complications							
667010107	45 F	LCM 200	Acetabulum fracture	Dose not changed	R	1	0
755118512	53 F	LCM 200	Concussion (brain)	WITHDRAWN	R	52	200
754012804	66 M	LCM 400	Lower limb fracture	Dose not changed	R	30	400
667015602	51 M	LCM 400	Radius fracture	Dose not changed	R	136	200
754010714	51 M	LCM 400	Subdural hematoma	Dose not changed	R	10	200
667011801	25 F	LCM 400	Fluctuating intoxicat symptoms	WITHDRAWN	R	43	400
Investigations							
754016102	20 M	Placebo	Blood glucose elevated	Dose not changed	R with sequela	75	0
754011214	41 M	LCM 400	Anticonvulsant level Increased (CBZ)	Drug interrupted	R	14	200
667017204	41 F	LCM 200	ECG abnormal	WITHDRAWN	R	29	0
755106406	61 M	LCM 200	ECG PR ↑	WITHDRAWN	R	1	100
755114408	43 M	LCM 200	Transaminase ↑	WITHDRAWN	Lost to FU	36	200
755124207	23 F	LCM 200	Hepatic enzymes ↑	WITHDRAWN	R	1	0

Source: AE Datasets in EP S1 submitted January 2008.

The cases of ECG and liver enzymes abnormal are reviewed later under AE of interest (7.1.4).

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- **Serious AEs in the EP Pool S2**

The overall incidence of SAEs in all LCM treated patients was greater in EP Pool S2 (17.9%) than EP Pool S1 (6.5%). This is not unexpected given the longer duration (exposure up to 5 years) in EP Pool S2. SAE with highest rates were again in the Nervous system (7.2%), followed by Injury, poisoning and procedural complications (3.1%) and Psychiatric disorders (2.2%) SOCs. Table 16 shows the overall incidence of SAE in EP Pools S1 and S2.

COMMENT: Given the study design of the open label phase, the analysis of safety in terms of dose-response in Pool S2 is challenging because of the lack of placebo and because the doses of LCM and concomitant medications were changed as needed. Additionally, the analysis by modal dose allows an event to appear in more than one dose group. The sponsor had submitted tables with SAE by modal dose (the most frequently received dose).

Table 16. Rate of Serious TEAEs in EP Pool S1 and S2

MedDRA System Organ Class Patients with at least one event	Pool EP S1 LCM Total, N=944 n (%)	Pool EP S2 LCM Total, N=1327 n (%)
Any system organ class	61 (6.5)	237 (17.9)
Blood and lymphatic system disorders	1 (0.1)	2 (0.2)
Cardiac disorders	1 (0.1)	11 (0.8)
Congenital, familial and genetic disorders	0	1 (<0.1)
Ear and labyrinth disorders	2 (0.2)	3 (0.2)
Endocrine	0	1 (<0.1)
Eye disorders	1 (0.2)	3 (0.2)
Gastrointestinal disorders	6 (0.6)	20 (1.5)
General disorders and admin site condit.	3 (0.3)	14 (1.1)
Hepatobiliary disorders	1 (0.1)	5 (0.4)
Immune system disorders	0	1 (<0.1)
Infections and infestations	5 (0.5)	16 (1.2)
Injury, poisoning and procedural complic.	5 (0.5)	41 (3.1)
Investigations	5 (0.5)	14 (1.1)
Metabolism and nutrition disorders	2 (0.2)	7 (0.5)
Musculoskeletal and connective tissue	2 (0.2)	9 (0.7)
Neoplasm, malignant and unspecified	3 (0.3)	11 (0.8)
Nervous system disorder	20 (2.1)	95 (7.2)
Pregnancy, puerperium and perinatal	1 (0.1)	2 (0.2)
Psychiatric disorders	7 (0.7)	29 (2.2)
Renal and urinary disorders	2 (0.2)	5 (0.4)
Reproductive system and breast disorders	1 (0.1)	6 (0.5)
Respiratory, thoracic and mediastinal dis.	2 (0.2)	12 (0.9)
Skin and subcutaneous tissue disorders	0	4 (0.3)
Social circumstances	0	1 (<0.1)
Surgical and medical procedures	0	11 (0.8)
Vascular disorders	1 (0.1)	5 (0.4)

Pool S2: Patients allowed to change dose of LCM and concomitant AEDs, or have surgery; some patients in Pool S2 had been on LCM for up to 5 ½ years. Source: Sponsor's tables.

SAE in Pool EP S2 by modal dose is presented in Appendix 3. Serious TE AEs by modal dose for the three most common SOCs are presented in Appendix 4 (Nervous System disorders), Appendix 5 (Psychiatric disorders) and Appendix 6 (Injury, poisoning and procedural complications).

Altogether, in pool S2 there were 16 fracture-related terms, as compared to 3 in the placebo-controlled period. In addition to trauma during seizure activity, these fractures could be related to dizziness or ataxia. Again, the lack of a control arm makes difficult to interpret 16 fractures. Of note, there were no relevant bicarbonate changes in EP S2.

Of note, there was one additional attempted suicide, two additional cases of serious hallucination, and three additional serious cases of psychosis-related adverse events during the open label period of the phase 2/3 studies. This information is difficult to interpret in the presence of changes of concomitant medications and the absence of a control arm.

- **SAEs for LCM phase 2/3 oral capsule formulation in patients with partial onset epilepsy**

There were three serious AEs in study SP586 (Table 17) and no serious AEs in study SP598.

Table 17. Lacosamide. Treatment emergent Serious Adverse Events in studies with oral capsule

ID	Age Gender	Tr Group	PT	Action	Out come	Rel study day	Comment
SP586/3001	23, F	LCM 200	Migraine	No	No R	1	On Gabapentin and Valproate. Unlikely related
SP586/3003	32, M	LCM 500	Vomiting	No	R	1	Lamotrigine and phenytoin. Probably related.
SP586/3007	29, M	LCM 600	Hallucinations (Visual)	Dose ↓ to 400	R	15	See narrative below

- **Subject 3007** was a 29-year-old white male. His medical history included blackout (1995) and depression (unknown). He began treatment with lacosamide 200mg/day on 02 Dec 1999. At the time of the serious adverse event, the subject was taking lacosamide 600mg/day and had been at this dose level for 2 days. He experienced visual hallucinations of moderate intensity. Diagnostic tests performed on the day of the event including complete blood count, blood chemistry and urinalysis were within normal limits. The subject was treated with intravenous lorazepam 1 mg and recovered on 18 Dec 1999. Trial medication was reduced from 600mg/day to 400mg/day. The subject received his final administration of trial medication on 29 Dec 1999. Concomitant medications at the onset of the serious adverse event included felbamate (an exclusionary medication in phase 2/3 studies) and carbamazepine.

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COMMENT: The development of hallucinations in a patient who had not received any other new medication during the study is of concern. Several cases of hallucinations have also been observed in the phase 2/3 oral tablet studies. The finding suggests some potential for abuse. The oral capsule study had a faster titration schedule and was less well tolerated.

- SAE for LCM IV infusion

- Phase 1 IV infusion

There was one SAE of epiglotittis during a phase 1 IV study. This AE was unlikely related to LCM.

- Phase 2/3 IV infusion

There was 1 SAE reported during the SP757 trial (Subject 170106). This SAE of **bradycardia** occurred during a 15-minute infusion on Day 2 of IV LCM. The narrative is as follows:

- **Subject 757170106** was a 48 year old white male with a prior history of hypertension. He was randomized to oral LCM 200 mg/day on 5/9/05. He completed the 12-week phase and was rolled over into OLE SP774. He began oral LCM 200 on 9/13/05. He was then enrolled in the OL SP757 on 3/22/06. At the time of enrollment in the IV trial, he had been taking oral LCM 300 mg/day for 74 days. At the time of the serious AE of bradycardia, he had received two IV infusions (total, LCM 300 mg/day). He received IV LCM 150 mg dose at an infusion rate of 1mL/minute (min) over 15 minutes in the morning and evening, on 3/23/06 without any AE. A mild effect in the PR interval was observed during the first infusion on day 1 (from 190 ms at pre-dose to 204 ms 7.5 min later) but no effect was observed during the second infusion.

  On 3/24/06 (third infusion) his HR predose was 62 bpm, with a BP of 120/80 mmHg; ECG showed PR= 188 ms, QRS 96 ms and QTc(B) 410 ms. Approximately 7 minutes into the infusion, the subject's heart rate dropped to 26bpm with a blood pressure of 100/60mmHg. The investigator reported that the subject became pale and weak (preceded by a period of hot and painful limbs and head). The LCM infusion was stopped due to the AE. The ECG changes were reported to be resolved 4 minutes after onset. There was no prolongation of the PR or QRS intervals at the time of the bradycardia. The changes disappear by min 15 (after infusion stopped). The subject was withdrawn from SP757 and restarted his oral dose of LCM (150 mg) the evening of 3/24/06. His physical exam results at the end of the trial (3/29/06) were normal. Concomitant medications included perindopril 2 mg/day, acebutolol 200 mg/day and carbamazepine 1200 mg/day.

  Two cardiologists evaluated this serious adverse event and concluded that this case could either be a sinus bradycardia with junctional escape, or an AV block with sinus exit block. The following is an excerpt of the cardiologists'evaluation of the event:

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ECGs before and after the event were normal except for sinus bradycardia. The ECG recorded during the event 24 March at — is technically poor, probably due to patient movement. It can reasonably be interpreted as sinus bradycardia, sinus pause, and junctional escape. Alternatively, there is a pattern to the P wave intervals that suggests sinus exit block, and possible P waves without QRS complexes that suggest blocked AV conduction.

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They conclude: "The event is typical of a vasovagal reaction, both in terms of the patient's symptoms and ECG presentation." "The occurrence of an event during IV infusion of experimental drug, which was not known to have occurred before in this patient raises concern that the drug is either fully responsible or at least plays a role in the event. Based on the pharmacology and previous human experience with LCM, neither bradycardia nor a primary vasovagal event would be expected. Expected CNS and GI side effects of LCM could possibly precipitate a vasovagal event but there is no evidence favoring this sequence of events. **AV block, possibly with sinus exit block would be a reasonable explanation based on lacosamide's known profile; however, it is not clear from the ECG tracing if that is what has occurred. Also it seems likely acebutolol played a role in this event.**"

Comment: This 48 year old male with prior history of HTN presented a marked decrease in SBP (from 140 to 100 mmHg) developed profound bradycardia (26 bpm) 7 ½ minutes into the third infusion. Two cardiologists who evaluated the case diagnosed it as either bradycardia with junctional escape, or an AV block with sinus exit block. Dr. Grant, the FDA cardiologist who evaluated the case believes this is likely a vasovagal reaction because of the rapid recovery.

In my opinion the event of hypotension and bradycardia around 7 minutes into de infusion are biologically plausibly LCM related. Non clinical studies in anesthetized dogs showed short lasting hypotension as well as PR and QRS prolongation 2-7 minutes after the infusion at doses equivalent to the 300 mg bid in humans (14.5 ± 1.7μg/mL). At higher doses, dogs showed AV block, IV dissociation and nodal rhythm. LCM levels -measured before dosing and after dosing, but not at the time of the AEs- were below 9μg/mL after the first two doses and a few minutes after the infusion was stopped, however, the patient was taking a beta blocker and that may have predisposed him to the LCM effects.

Very few patients (<5%) were taking concomitant beta blockers at baseline in EP S1. A total of 3 patients were taking a beta blocker among the 100 receiving the 15-minute IV infusion, and one of them, presented this case of profound bradycardia with an ECG suspicious of AV block with sinus exit block.

- Serious AEs in LCM phase 1 studies with oral formulation (tablet and capsule)

Across the 21 phase 1 trials, five subjects experienced SAEs, as follows:

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Table 18. Treatment emergent Serious Adverse Events in LCM phase 1 studies with the oral formulation

ID	Age Gender	Tr Group	PT	Action	Out come	Rel study day	Comment
588/ 8061	30, M	LCM 1000	Hepatitis & nephritis	none	R	post trial	See narrative below
620/ 16228	76, M	LCM 100 BID	HTN (also non-serious tremor & dyspepsia)	none	No R	3	No prior history of HTN. Tremor & dyspepsia likely related to LCM.
620/ 17917	76, M	Placebo	A. fibrillation	None WD	R R	5 1	No prior history of AFib. Not related to LCM.
644/ 80016	32, M	A: LCM B: placebo	Accident NOS	None	R	post trial	Digoxin interaction study. At 14-day safety FU after placebo, he had a cut wound on left forearm. Unlikely related.
640/ 82043	41, F	LCM 800 x 4 days	Spontaneous abortion	None	R	post trial	AE reported 9 days after completion. Negative BHCG on day before last dose.

The narrative of the case of drug induced hepatitis/nephritis hypersensitivity is presented below:

-Subject 588/8061 was a 30 year old male healthy volunteer, who was randomized to LCM 1000 mg/day (oral capsule) on Oct 24, 2000. He presented several episodes of dizziness 30 min to 1 hour after taking LCM (different doses, 400 to 1000 mg/daily). On day #4, the dose was reduced to 400 mg bid. He completed the trial and was discharged from the site on 11 Nov 2000. Laboratory tests up to that date were normal. His laboratory values were as follows:

Date	Visit	ALT/AST (U/I) <23/<21	ALP (U/I) <180	Bilirubin (mg/dL)
10/10/00	Screening	7/5	86	1.6
10/24/00	Day 1	4/6	86	1.6
10/26/00	Day 3	7/5	93	1.1
11/3/00	Day 11	9/5	98	0.9
11/8/00	Day 16	4/6	83	0.9
11/11/00	Day 19	11/3	92	1.2

On 21 Nov 2000, 12 days after the final dose of lacosamide, he experienced nausea, headache, and upper abdominal discomfort followed by fatigue and brown coloration of urine. Or ——— special diagnostics were performed in a hospital, and drug-induced hepatitis was suspected. Blood chemistry showed increased liver enzymes (AST/GOT 1550U/L, normal range below 40U/L; ALT/GPT 422U/L normal range below 40U/L; gamma-GT 982U/L, normal range 11-50U/L) along with proteinuria and casts (unknown values). Additional information was requested regarding bilirubin, however, as per the sponsor's response, no bilirubin was measured at the time of this AE.

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The results of the available tests at the time and after the events are summarized as follows:

Date	ALT/AST (U/L)	ALP (U/L)	Bilirubin (mg/dL)
—	385/128	NA	Not done
11/28/00	422/1550	NA	Not done
12/1/00	123/52	NA	1.3 (or 22 µmol/L)

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At trial entry, no recent history (6 months) of chronic alcohol or drug abuse was reported, and remote history of alcohol or drug abuse was not spontaneously reported. There were no concomitant medications at the onset of any of the above-mentioned adverse events.

The following tests for viral hepatitis were performed and were negative: HbsAg, HAV IgM, HAV IgG, HCV. The subject refused hospitalization and was therefore received outpatient treatment from — — He received five infusions of 10% glucose with vitamin C. The laboratory tests on — still revealed elevated liver enzymes (AST/GOT 1550U/I, ALT/GPT 422U/I, GGT 82U/I); protein in urine remained increased as well. As per the sponsor's response to an FDA request for information, bilirubin was not measured —

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As per the narrative submitted with the ISS, the laboratory tests on 01 Dec 2000 were: AST 52U/I, ALT 123U/I, GGT 11U/I, **bilirubin 22 mg/dL**; urine analysis was normal. Echocardiography and ECG did not reveal any pathologic findings. The suspected diagnosis was toxic hepatitis, toxic glomerulopathy. As per the sponsor evaluation of AE report dated February 28, 2005, submitted to the FDA via email on 5/23/08, the bilirubin on 01 December 2000 was 1.3 mg/dL (reported as **22 µmol/L**).

The subject was invited to the trial site on 19 Dec 2000 for an extended follow-up. The following examinations were performed: clinical examination, ECG, clinical laboratory tests (hematology, blood chemistry and urine analysis), blood examination for serology (HbsAg, HIV, HCV, hepatitis virus A-genome(RNA-PCR), hepatitis virus B-genome (DNA-PCR), hepatitis virus C-genome (AMPL-RNA PCR), cytomegalovirus genome (DNAPCR), and abdominal sonography. The subject was free of complaints, and no abnormal findings were observed in any of the clinical or laboratory examinations. Additionally, the subject consulted the — Hospital. The gastroenterologist diagnosed acute drug-induced hepatitis without any sequelae. **The dermatologist interpreted this event as a possible delayed allergic reaction toward the trial medication**. A lymphocyte transformation test (LTT) revealed a borderline reaction, i.e. stimulation index of 2.2 (positive: >2.5) toward lacosamide. The investigator considered these events to be possibly related to trial medication.

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In this patient, laboratory evaluations were normal at the time of the last dose of study medication. Clinical symptoms of hepatitis along with extremely elevated transaminases and proteinuria with casts, and negative hepatitis serology were diagnosed 12 days after study completion. Symptoms and chemistries came down to normal within one month after the diagnosis. It appears odd that for this only time the bilirubin was reported on µmol/L rather than mg/dL, however, these labs were done close to his home in — , not in — , where other labs were done.

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As per the CRF, the % of eosinophils rose from 0.4% at screening (10/19/00) to 1.3% on the last day of the study (10/11/00) (this value is still way below the normal limits for the lab [7%]). It is unclear when and how much proteinuria the patient had. There are no laboratories in the CRF after November 11, 2000. It is unfortunate that the bilirubin and prothrombin time were not measured in November —. Transaminases are markers of hepatocellular damage, but not of liver function. A bilirubin >2x ULN would fulfill Hy's law and imply a high mortality risk. Of note, the patient received doses up to 1000 mg daily. The fact that the drug was stopped because of study completion may have prevented the patient for having more severe/irreversible hepatic damage.

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I agree with the investigator that this case is consistent with delayed drug-induced hepatitis. Moreover, the fact that nephritis was also diagnosed, it makes a potential case of a multi-organ or DRESS syndrome (Drug reaction with eosinophilia and systemic symptoms).

In summary, In EP S1, the overall rate of TE SAE is higher with LCM as compared to placebo (6.5% and 3.8%, respectively). Interpretation of a dose-response relationship in this database is hampered by the forced titration study design and the smaller number of patients exposed doses above 400 mg/day dose. The most common SAE in EP S1 and EPS2 were Nervous system disorders (mostly convulsions) and Psychiatric disorders SOCs. Interpretation of causality is confounded by the fact that patients with epilepsy are at increased risk for developing AE in both SOCs. One case of syncope that appeared to be related to study medication (although with no clear mechanism) was reported in this population. In the multiple dose IV LCM study (SP757) there was a case of profound bradycardia (26 bpm) during the 15 minutes infusion, with a question of a sinus bradycardia with junctional rhythm versus a sinus exit block. One serious case of hepatitis/ nephritis hypersensitivity was reported in one phase 1 study with LCM oral capsule. Of note, in the DNP database, the highest proportions of SAEs was in the cardiac disorders SOC.

Most frequent TE SAEs in the DPN population belonged to the cardiac disorder system SOC (angina, coronary artery disease, A-fib, A-flutter, and bradycardia) and the nervous system disorder SOC (loss of consciousness and transient ischemic attack). Overall, SAEs were slightly higher in the LCM treated patients (7.5%) compared to the placebo (5.2%). The frequency of the cardiac SAEs was similar between the LCM and placebo treated patients (2.5% vs. 2.9%, respectively). However, most of the cardiac conduction/rhythm abnormalities recorded as SAEs were reported from subjects treated with LCM. Other significant adverse events that were observed to occur more frequently in patients receiving LCM compared to placebo were syncope related events (7.3% vs. 2.4%, respectively). Most cases of syncope did not have ECG evaluations at the time or after the event. The small number of syncopal events with evidence of possible cardiac etiology occurred at a LCM dose of 600 mg/day. For details the reader is referred to Dr. Pokrovnichka's clinical review.

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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts (EP S1)

Across the placebo-controlled trials in subjects with partial-onset seizures, there was a clear dose-dependent increase in premature discontinuations with increasing doses of LCM. Overall, 8.2%, 10.7%, 17.1%, and 34.7% of subjects discontinued because of AEs in the placebo, LCM 200mg/day, LCM 400mg/day, and LCM 600mg/day groups, respectively. The majority of patients who discontinued due to AEs did so during the titration period, particularly for the LCM 400 and 600 mg/day doses. There were very few discontinuations during the transition and tapering phases. Of note, patients were allowed to undergo one step dose reduction in case of intolerance because of an AE. If there was need for a second dose reduction, the patient was to be discontinued. A total of 331 adverse events in 188 subjects led to discontinuation from EP Pool S1 (all phases: treatment, taper and transition), 20 from the placebo treatment group and 168 from the LCM treatment group. In the placebo group, there were 12 female & 8 males, ages 22 to 63 years (median 41). In the LCM treated group, there were 114 females & 54 males, ages 18 to 70 years (median 41).

7.1.3.2 Adverse events associated with dropouts (EP S1)

A summary table of AE that led to discontinuation in EP S1 by SOC is presented in Table 19.

Table 19. Lacosamide NDA. Dropouts due to AEs, during treatment phase by randomized dose in EP S1

MedDRA System Organ Class	Placebo (N=364) n (%)	LCM (mg/day)			
		200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Any system organ class	18 (4.9)	22 (8.1)	81 (17.2)	58 (28.6)	161 (17.1)
Blood and lymphatic system disorders	0	2 (0.7)	1 (0.2)	0	3 (0.3)
Cardiac disorders	0	1 (0.4)	3 (0.6)	0	4 (0.4)
Ear and labyrinth disorders	0	3 (1.1)	5 (1.1)	5 (2.5)	13 (1.4)
Eye disorders	1 (0.3)	5 (1.9)	13 (2.8)	10 (4.9)	28 (3.0)
Gastrointestinal disorders	3 (0.8)	3 (1.1)	15 (3.2)	12 (5.9)	30 (3.2)
General disorders and admin site condit.	1 (0.3)	2 (0.7)	6 (1.3)	8 (3.9)	16 (1.7)
Hepatobiliary disorders	0	0	1 (0.2)	1 (0.5)	2 (0.2)
Infections and infestations	0	0	0	1 (0.5)	1 (0.1)
Injury, poisoning and procedural complic.	0	1 (0.4)	1 (0.2)	2 (1.0)	4 (0.4)

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MedDRA System Organ Class	Placebo (N=364) n (%)	LCM (mg/day)			
		200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Investigations	1 (0.3)	5 (1.9)	3 (0.6)	1 (0.5)	9 (1.0)
Metabolism and nutrition disorders	0	0	1 (0.2)	1 (0.5)	2 (0.2)
Musculoskeletal and connective tissue dis.	1 (0.3)	1 (0.4)	1 (0.2)	3 (1.5)	5 (0.5)
Neoplasms benign, malignant and Unspecified (incl cysts and polyps)	1 (0.3)	1 (0.4)	0	0	1 (0.1)
Nervous system disorder	9 (2.5)	6 (2.2)	43 (9.1)	44 (21.7)	93 (9.9)
Psychiatric disorders	0	1 (0.4)	10 (2.1)	4 (2.0)	15 (1.6)
Respiratory, thoracic and mediastinal dis.	0	0	1 (0.2)	0	1 (0.1)
Skin & SC tissue disorders	2 (0.5)	0	5 (1.1)	1 (0.5)	6 (0.6)
Vascular disorders	1 (0.3)	0	0	0	0

Note: Treatment Phase includes both Titration and Maintenance Phase data. n = Number of subjects who reported at least one event during the phase. % = Percent with respect to the number of subjects in Pool S1.
Source: Sponsor Table, Summary of Clinical Safety. Table EP 6.29.1.

More patients presented treatment emergent AE that led to dropout in the LCM group (overall 17.1 %) as compared to placebo (4.9%) .The analysis of AE dropouts by randomization dose shows a clear dose response, particularly for the SOCs with the largest numbers of events. The SOCs with higher overall rates of discontinuation are the Nervous system disorders (9.9%), GI disorders (3.2%), General, site and administration disorders (3.0%), Eye disorders (1.7%), Psychiatric (1.6 %) and Ear and labyrinth disorders (1.4%).

The following table shows patients who discontinued due to AEs from the EP Pool S1 by the time of onset of the AE (not by randomization dose, as presented in other tables).

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Table 20. Lacosamide NDA. Incidence of treatment emergent AEs that led to early discontinuation in at least 1% of patients in any treatment group, by SOC, during treatment phase in EP Pool S1, by dose at AE onset

MedDRA System Organ Class	LCM (mg/day)						
	Placebo (N=781) n (%)	100 (N= 938) n (%)	200 (N=897 n (%)	300 (N=626) n (%)	400 (N=603) n (%)	500 (N=165) n (%)	600 (N=155) n (%)
Any system organ class	23 (2.9)	23 (2.5)	29 (3.2)	30 (4.8)	40 (6.6)	12 (7.3)	6 (3.9)
Blood and lymphatic system disorders	1	1	0	0	0	0	0
Ear and labyrinth disorders	1	2	3	5 (0.8)	1	0	0
Eye disorders	0	7 (0.7)	8 (0.9)	4 (0.6)	9 (1.5)	1 (0.6)	1 (0.6)
Gastrointestinal disorders	6	5 (0.5)	4	2	12 (2.0)	2 (1.2)	1 (0.6)
General disorders and admin site condit.	3	2	1	4	2	2	0
Injury, poisoning and procedural complic.	0	0	1	0	0	1	0
Investigations	1	1	1	0	0	0	0
Musculoskeletal and connective tissue	0	1	1	0	1	1 (0.6)	0
Nervous system disorder	13 (1.7)	11 (1.2)	17 (1.9)	22 (3.5)	25 (4.1)	9 (4.9)	5 (3.2)
Psychiatric disorders	1	2	1	0	2	1	0
Skin and subcutaneous tissue disorders	2	0	1	1	2	0	0

Note: If a subject has more than one occurrence of the same AE with different doses at onset, the adverse event is summarized under each applicable dose at onset. Common AEs are defined as those AEs occurring in at least 1% of subjects in any of the LCM treated groups within Pool S1. Note: Treatment Phase includes both Titration and Maintenance Phase data. Note: n = Number of subjects who reported at least one event during the phase. % = Percent with respect to the number subjects for whom the dose was administered during the phase. [1] Common: occurring in at least 1% of subjects in any treatment group. Source: Sponsor table EP.6.47.1 (The sponsor did not provide a table of discontinuation for all AEs by dose at onset of AE)

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Of note, subjects randomized to receive LCM 200 or 400 mg/day received placebo for 4 weeks or 2 weeks, respectively. The sponsor uses 781 as the denominator in tables presenting data by dose at onset because 781 subjects received placebo at least once during the double-blind, placebo-controlled trials (Source: Sponsor's response to FDA request of clarification, submitted 2/11/08).[6]

> *The data indicate a clear dose-response up to the 500 mg/day dose, but suggest a lower rate of dropouts for the 600 mg/day dose. Interpretation of the data is hampered by the fact that the dose at onset of the event may not have been the dose at time of dropout, and that fewer patients were exposed to doses >400 mg/day.*

The following table presents the AE leading to discontinuation by preferred terms for Nervous System disorders SOC by randomization dose.

Table 21. Lacosamide NDA. Patients who discontinued from EP Pool S1, by preferred term in the Nervous system disorders SOC during the treatment phase by randomized dose

MedDRA System Organ Class Nervous system disorder	Placebo (N=364) n (%)	LCM (mg/day)			
		200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Any	9 (2.5)	6 (2.2)	43 (9.1)	44 (21.7)	93 (9.9)
Dizziness	2 (0.6)	1 (0.4)	20 (4.2)	35 (17.2)	56 (5.9)
Coordination abnormal*	0	1 (0.4)	6 (1.3)	11 (5.4)	18 (1.9)
Convulsion	4 (1.1)	2 (0.7)	8 (1.7)	0	10 (1.1)
Tremor	0	0	3 (0.6)	5 (2.5)	8 (0.8)
Nystagmus	0	0	1 (0.2)	5 (2.5)	6 (0.6)
Headache	0	0	4 (0.8)	2 (1.0)	6 (0.6)
Balance disorder	0	0	2 (0.4)	2 (1.0)	4 (0.4)
Somnolence	2 (0.6)	1 (0.4)	1 (0.2)0	2 (1.0)	4 (0.4)
Memory impairment	0	1 (0.4)	0	2 (1.0)	3 (0.3)
Disturbance in attention	0	0	1 (0.2)0	2 (1.0)	2 (0.2)
Hypoesthesia	0	1 (0.4)	0	0	2 (0.2)
Amnesia	0	0	0	1 (0.5)	1 (0.1)
Cognitive disorder	0	0	0	1 (0.5)	1 (0.1)
Mental impairment	0	0	0	1 (0.5)	1 (0.1)
Movement disorder	0	0	1 (0.2)	1 (0.5)	1 (0.1)
Paresthesia	0	0	1 (0.2)	1 (0.5)	1 (0.1)
Grand mal convulsion	1 (0.3)	0	1 (0.2)	0	2 (0.2)

[6] On a subsequent request for clarification, the sponsor provided an updated number of 736, based on patients who were on placebo before starting LCM but not included patients who missed one day of LCM treatment while randomized to LCM. Analyses using 736 as the denominator would yield slightly higher placebo rates, but they will not be re-calculated in this review.

b(4)

MedDRA System Organ Class Nervous system disorder	Placebo (N=364) n (%)	LCM (mg/day)			
		200 (N=270) n (%)	400 (N=471) n (%)	600 (N=203) n (%)	LCM Total (N=944) n (%)
Basilar migraine	0	0	1 (0.2)	0	1 (0.1)
Cerebellar syndrome	0	0	1 (0.2)	0	1 (0.1)
Clumsiness	0	0	1 (0.2)	0	1 (0.1)
Dysarthria	0	0	1 (0.2)	0	1 (0.1)
Lethargy	0	0	1 (0.2)	0	1 (0.1)
Nervous system disorder	0	0	0	0	1 (0.1)
Status epilepticus	0	0	0	0	1 (0.1)
Complex partial seizures	1 (0.3)	0	0	0	0
Muscle contractions involuntary	1 (0.3)	0	0	0	0
Sedation	1 (0.3)	0	0	0	0

Note: Treatment Phase includes both Titration and Maintenance Phase data. Note: n = Number of subjects who reported at least one event during the phase. % = Percent with respect to the number of subjects in Pool S1. Source, Summary of Clinical Safety, Table EP.6.29.1. * Coordination abnormal includes mostly ataxia.

The most common AE leading to discontinuation in the Nervous System disorders was dizziness, followed by ataxia and convulsions.

- Dropouts due to dizziness in EP S1

Dropout due to dizziness was 4-fold most common in the LCM 600 randomization group, as compared to the LCM400 group (17% vs. 4%) and 30-fold more common as compared to LCM 200 or placebo. The mean and median dose at the time of onset of the AE was 300 mg/day. Most of the cases of dizziness that led to discontinuation were moderate to severe in intensity and occurred during the titration phase. Twenty two were severe and three were serious (all the serious cases occurred at the highest dose). Of note, most patients did not have isolated dizziness, but had other accompanying symptoms such as vomiting, nystagmus, fatigue, tremor, etc. Dizziness is very common with other AEDs as well.

> *Orthostatic blood pressure was not measured systematically in phase 2/3 trials and was not measured in most cases of dizziness. However, orthostatic changes were measured in SP640. No evidence of orthostatic changes was found in this study. If any future study is done with LCM, it would be advisable to include OH measurements in cases of dizziness and syncope.*

-Dropouts due to Ataxia/Coordination abnormal in EP Pool S1.

A total of 25 patients discontinued from the placebo-controlled studies because of cerebellar and coordination disorders (mostly ataxia and nystagmus). None of the patients who withdrew from the studies because of AEs were randomized to placebo. They were 4 male and 19 female, ages 27 to 64 years (mean 41). The mean number of days on treatment at the time of the event was 23

days (range 1 to 41). The mean LCM dose at the time of the onset of the AE was 307 mg/day. Two out of the 25 patients randomized to LCM who discontinued the trial because of these events had not started LCM when the events occurred and 23 were taking LCM doses of 100 to 600 mg/day. Accounting for the patients who had the AE while on placebo, the rate of discontinuation under the MedDRA Cerebellar coordination and balance disorders High Level Term (HLT) is 2.4% (23/944) for LCM and 0.3% (2/718) for placebo. These patients are listed in the following table.

Table 22. Lacosamide. Dropouts due to AE under the MedDRA Cerebellar coordination and balance disorders HLT in EP S1

ID	TrtGrp	AE term	PT	Outcome	Rel st day	AE DOSE
667018802	LCM 200	Ataxia	Coordination abnormal	R	42	0
667013202	LCM 200	Ataxia	Coordination abnormal	R	31	300
667015704	LCM 400	Unsteady gait after morning dose,ataxia	Coordination abnormal	Ongoing	26	0
667018818	LCM 400	Poor balance	Balance disorder	R	39	400
667019104	LCM 400	Unsteadiness developing over 2 days	Balance disorder	Unknown	30	300
754011009	LCM 400	Ataxia	Coordination abnormal	R	18	300
754018302	LCM 400	Ataxia	Coordination abnormal	R	24	400
	LCM 400	Nystagmus	Nystagmus	R	29	400
754018304	LCM 400	Ataxia	Coordination abnormal	R	21	300
754018401	LCM 400	Ataxia	Coordination abnormal	R	26	400
755116204	LCM 400	Cerebellar syndrome	Cerebellar syndrome	R	18	300
667010111	LCM 600	Ataxia, unsteadiness	Coordination abnormal	R	2	100
667010202	LCM 600	Ataxia-broad based (Serious)	Coordination abnormal	Ongoing	3	100
	LCM 600	Nystagmus (Ser)	Nystagmus	R	8	100
667011806	LCM 600	Ataxia	Coordination abnormal	R	23	400
667012504	LCM 600	Ataxia	Coordination abnormal	R	9	200
	LCM 600	Nystagmus	Nystagmus	R	9	200
667012806	LCM 600	Gait ataxia	Coordination abnormal	R	30	400
667015103	LCM 600	Ataxia	Coordination abnormal	R	23	300
667015401	LCM 600	Gait ataxia	Coordination abnormal	R	44	500
667016001	LCM 600	Nystagmus	Nystagmus	R	19	300
667016104	LCM 600	Nystagmus (Ser)	Nystagmus	R	41	600
667016935	LCM 600	↓ Coordination	Coordination abnormal	R	29	400
	LCM 600	Nystagmus	Nystagmus	R	29	400
667018808	LCM 600	Ataxia	Coordination abnormal	R	29	400
754012806	LCM 600	Balance difficulty	Balance disorder	R	21	300
754018301	LCM 600	Ataxia	Coordination abnormal	R	41	600
754018901	LCM 600	Ataxia	Coordination abnormal	R	10	200

b(4)

As noted in this table, the sponsor wrongly coded the LLT ataxia to the PT "Coordination Abnormal", when it should be coded to the PT "Ataxia."

Of note, the PTs "tremor" and "intention tremor" are not included under the MedDRA Cerebellar coordination disorders HLT, but under the "Tremor (excluding congenital" HLT, and the "Movement disorders (including parkinsonism)" HLGT. The following table lists the patients who discontinued due to tremor, along with other AEs listed around the same time.

Table 23. Dropouts due to tremor in EP S1

USUBJID	TRTGRP	AETERM //other AEs	OUTCOME	CRELSTDY	AEDOSE
754018302	LCM 400	Tremor //ataxia, nystagmus, mental status change	R	29	400
755110606	LCM 400	Tremor-postural//fatigue	recovering/resolving	15	200
755122201	LCM 400	Shakiness	R	23	400
667010111	LCM 600	Tremulousness//ataxia, drowsiness, altered mental status//double vision	R	2	100
667010202	LCM 600	Tremor-at rest and increased with finger nose finger// poor balance/lightheadedness	ongoing	3	100
667012806	LCM 600	Tremor//ataxia, nystagmus	R	31	400
754013504	LCM 600	Tremor//insomnia, decreased concentration, anticonvulsant toxicity, itching	R	9	200
754018901	LCM 600	Increased tremor//dizziness, ataxia, Romberg worsening	not resolved	10	200

Source: AE datasets, EP S1, submitted January 2008. R= resolved. AE DOSE= dose at onset of AE

All 8 cases of tremor leading to discontinuation occurred during the titration phase, all in subjects taking LCM. Most of the cases of tremor are associated with cerebellar signs/symptoms. Three were in the LCM 400 randomization group, and four were in the LCM 600 randomization group. Duration of the event for those with information was 1 day to 98 days. Three subjects had not recovered by the time of last follow up.

- Dropout due to seizure-related AEs

The percentage of discontinuations due to a seizure-related AE was the same for overall LCM vs. placebo. The term convulsion generally refers to increased rate of seizures but does not specify whether it was a partial seizure or a generalized seizure. If we combine all seizure activity we get the following results: