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Table 24: Seizure-related AE dropouts in LCM in EP S1, treatment phase

MedDRA PT term	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	4 (1.1)	2 (0.7)	10 (2.1)	0	12 (1.3)
Convulsion	4 (1.1)	2 (0.7)	8	0	10
Status epilepticus	0	0	2	0	2

Source, Summary of Clinical Safety, Table EP.6.29.1.

The overall rate of cases of seizure activity leading to discontinuation in this database is similar between placebo and LCM treated patients. It is unclear why LCM 400 appears to have a higher rate than the LCM 200 and LCM 600 groups. The listing of cases in which seizure activity led to a study discontinuation is presented as follows:

Table 25. Lacosamide. Dropouts due to seizure-related adverse event EP Pool S1

ID	TrtGroup	AE term	LLT	PT	Rel st day	Serious	Outcome	AE dose
667015009	Placebo	Increase of Sz frequency	Convulsions aggravated	Convulsion	100	Yes	R with sequelae	0
754012010	Placebo	Increased of seizures	Convulsions aggravated	Convulsion	2	No	R	0
754018303	Placebo	Flurry of seizures	Convulsions aggravated	Convulsion	41	No	R	0
755118104	Placebo	Seizures increase	Convulsions aggravated	Convulsion	82	No	R	0
667011910	LCM 200	Increased number of Sz	Convulsions aggravated	Convulsion	1	Yes	R	0
755118617	LCM 200	Seizures increase	Convulsions aggravated	Convulsion	26	No	R	200
667010404	LCM 400	Seizures	Seizures	Convulsion	99	Yes	R	400
667014801	LCM 400	Worsening Sz change in "aura"	Convulsions aggravated	Convulsion	17	No	R	100
754010107	LCM 400	Status epilepticus	Status epilepticus	Status epilepticus	31	Yes	R	400
754013604	LCM 400	Increased Sz frequency, hospitalization	Convulsions aggravated	Convulsion	1	Yes	R	100
754017202	LCM 400	Worsening of seizures	Seizure	Convulsion	21	No	R	300
754019001	LCM 400	Increased Sz frequency	Convulsions aggravated	Convulsion	20	No	R	300
755108202	LCM 400	Hospitalization status epileptic	Status epilepticus	Status epilepticus	123	Yes	R	0
755118106	LCM 400	Seizures increase	Convulsions aggravated	Convulsion	31	No	R	400
755118211	LCM 400	Seizures increase	Convulsions aggravated	Convulsion	3	No	R	100

ID	TrtGroup	AE term	LLT	PT	Rel st day	Serious	Outcome	AE dose
755118613	LCM 400	Increase of seizures	Convulsions aggravated	Convulsion	13	No	No RE	200

LLT= MedDRA lower level term. Source: AE datasets in EP S1.

The mean and median doses at the time of the onset of the AE of seizure among patients randomized to LCM were 208 mg/day and 200 mg/day, respectively. No seizure-related events occurred in patients while receiving 500 and 600 mg/day. This is reassuring, as higher doses of LCM do not seem to be associated with an increased risk of seizures leading to dropout.

- Dropouts due to AEs in other SOCs

Table 26 summarizes PT terms for AEs in other SOCs with >1% incidence of discontinuations.

Table 26. Lacosamide NDA. Patients who discontinued from EP Pool S1, by preferred term in selected SOCs1, during the treatment phase by randomized dose.

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 (%)
Gastrointestinal disorders	3 (0.8)	3 (1.1)	15 (3.2)	12 (5.9)	30 (3.2)
Vomiting	3	1	11 (2.3)	6 (3.0)	18 (1.9)
Nausea	1	1	8 (1.7)	8 (3.9)	17 (1.8)
Flatulence	1	0	1	1	2
Diarrhea	0	0	1	0	1
Pancreatitis	0	0	1	0	1
Abdominal pain/ abd pain upper	1	1	0	0	1
Dry mouth	0	1	0	0	1
Eye disorders	1 (0.3)	5 (1.9)	13 (2.8)	10 (4.9)	28 (3.0)
Diplopia	1	4 (1.5)	10 (2.1)	4 (2.0)	18 (1.9)
Vision blurred	0	1	3	6 (3.0)	10 (1.1)
Photopsia	0	0	1	0	1
General disorders and admin site condit.	1 (0.3)	2 (0.7)	6 (1.3)	8 (3.9)	16 (1.7)
Fatigue	1	0	3 (0.7)	3 (1.5)	6
Asthenia	0	0	0	4 (2.0)	4
Chest pain	0	2	0	1	3
Malaise	0	0	2	0	2
Feeling cold	0	0	0	1	1
Feeling abnormal	0	0	1	0	1
Feeling drunk	0	0	1	0	1

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 (%)
Psychiatric disorders	0	1 (0.4)	10 (2.1)	4 (2.0)	15 (1.6)
Depression/depr. Suicidal /suic. attempt	0	1	3	1	5
Confusional state/Mental status changes	0	0	4	0	4
Insomnia	0	0	0	1	1
Tearfulness	0	0	0	1	1
Bradyphrenia	0	0	0	1	1
Euphoric mood	0	0	1	0	1
Psychotic disorder	0	0	1	0	1
Ear and labyrinth disorders (All Vertigo or Vestibular disorders)	0	3 (1.1)	5 (1.1)	5 (2.5)	13 (1.4)
Skin and subcutaneous tissue disorders	2 (0.5)	0	5 (1.1)	1 (0.5)	6 (0.6)
Rash	2 (0.2)	0	2 (0.4)	0	2 (0.2)
Pruritus	0	0	0	1 (0.5)	1 (0.1)
Hyperhidrosis	0	0	1 (0.2)	0	1 (0.1)
Night sweats	0	0	1 (0.2)	0	1 (0.1)
Urticaria	0	0	1 (0.2)	0	1 (0.1)

1 SOCS with ≥ 1% discontinuations (other than the Nervous System) in at least one treatment group. 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.

Most of the GI and eye disorders leading to dropout are likely related to LCM. The cases of pancreatitis and peritonitis have been mentioned under SAEs and did not appear to be drug related. Asthenia, fatigue, malaise have been observed in phase 1 studies and are likely related to LCM. Psychiatric AEs and Skin rash and hypersensitivity will be discussed later under section 7.1.4 (AE of interest).

A table summarizing AE that led to discontinuations in SOCs that had an incidence <1.0% in EP S1 is in Appendix 7.

There were few dropouts due to cardiac disorders in the epilepsy population. They all occurred in the LCM treatment group. These cases are discussed in Section 7.1.4.1.of this review (AE of interest, Cardiac AEs).

Of note, in the placebo-controlled DPN studies five patients discontinued the study because of syncope/loss of consciousness. All five cases occurred in the LCM treatment group at doses of 400 and 600 mg/day (5/1023= 0.5% among LCM-treated patients and 0% among placebo). For details the reader is referred to Dr. Pokrovnichka's clinical review.

7.1.3.3 Adverse events leading to dose reduction in EP S1

On Feb 19, 2008, at the FDA's request, the sponsor submitted a summary table of TEAE that led to either dose reduction or discontinuation in all three placebo controlled studies (See Table below).

This analysis (by randomization dose) shows a dose response in terms of AE leading to dose reduction particularly for those SOCs with the larger numbers of events. Overall approximately half of AE that required dose reduction underwent discontinuation. Depending on the SOC, a different fraction of cases that underwent dose reduction ended up requiring discontinuation. The SOC that most led to dose reduction/discontinuation was the Nervous System Disorders SOC (18.6%) followed by Eye disorders (7.2%) and GI disorders (5.1%). Approximately half of the patients who required dose reduction ended up being withdrawn from the studies.

> *Comment: A summary table for AE that led to dose reduction in the epilepsy studies by randomization dose was submitted with the original application for SP754 and SP755 only. Dose reduction in study SP667 (US and non-US) had not been not prospectively identified/analyzed. Information from all three studies was submitted later in February 2008.*

A summary of TAE that led to dose reduction or dropout in EP Pool S1, treatment phase, by SOC and randomization dose is presented in the next table.

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Table 27. TAE that led to dose reduction or discontinuation in EP Pool S1, treatment phase, by SOC and randomization dose

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	26 (7.1)	42 (15.6)	141 (29.9)	94 (46.3)	277 (29.3)
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	5 (1.9)	12 (2.5)	6 (3.0)	23 (2.4)
Endocrine disorders	0	1 (0.4)	0	0	1 (0.1)
Eye disorders	1 (0.3)	9 (3.3)	32 (6.8)	27 (13.3)	68 (7.2)
Gastrointestinal disorders	4 (1.1)	7 (2.6)	23 (4.9)	18 (8.9)	48 (5.1)
General disorders and admin site condit.	2 (0.5)	4 (1.5)	17 (3.6)	12 (5.9)	33 (3.5)
Hepatobiliary disorders	0	0	1 (0.2)	1 (0.5)	2 (0.2)
Infections and infestations	0	0	5 (1.1)	1 (0.5)	6 (0.6)
Injury, poisoning and procedural complic.	0	1 (0.4)	3 (0.6)	2 (1.0)	6(0.6)
Investigations	1 (0.3)	5 (1.9)	7 (1.5)	3 (1.5)	15 (1.6)
Metabolism and nutrition disorders	0	2 (0.7)	1 (0.2)	1 (0.5)	4 (0.4)
Musculoskeletal and connective tissue dis.	1 (0.3)	1 (0.4)	3 (0.6)	3 (1.5)	7 (0.7)
Neoplasms benign, malignant and Unspecified (incl cysts and polyps)	1 (0.3)	1 (0.4)	0	0	1 (0.1)
Nervous system disorder	14 (8.0)	21(7.8)	84 (17.8)	71 (35.0)	176 (18.6)
Psychiatric disorders	0	3 (1.1)	14 (3.0)	5 (2.5)	22 (2.3)
Respiratory, thoracic and mediastinal dis.	0	0	1 (0.2)	0	1 (0.1)
Skin & SC tissue disorders	2 (0.5)	0	7 (1.5)	1 (0.5)	8 (0.8)
Vascular disorders	1 (0.3)	1 (0.4)	0	0	1 (0.1)

Source: February 19, 2008 response to FDA request for information.

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- AE dropouts in EP Pool S2

As seen in Table 28, overall, a similar percentage of subjects prematurely discontinued from the trials due to a TEAE in EP Pool S2 in comparison to EP Pool S1 for most SOCs.

Table 28. Rate of Discontinuations due to TEAEs in EP Pool S1 and S2, treatment phase

MedDRA System Organ Class	EP Pool S1 LCM Total (N=944) n (%)	EP Pool S2 LCM Total (N=1327) n (%)
Any system organ class	161 (17.1)	243 (18.3)
Blood and lymphatic system disorders	3 (0.3)	2 (0.2)
Cardiac disorders	4 (0.4)	7 (0.5)
Ear and labyrinth disorders	13 (1.4)	15 (1.1)
Eye disorders	28 (3.0)	34 (2.6)
Gastrointestinal disorders	30 (3.2)	34 (2.6)
General disorders and admin site condit.	16 (1.7)	24 (1.8)
Hepatobiliary disorders	2 (0.2)	2 (0.2)
Infections and infestations	1 (0.1)	2 (0.2)
Injury, poisoning and procedural complic.	4 (0.4)	11 (0.8)
Investigations	9 (1.0)	13 (1.0)
Metabolism and nutrition disorders	2 (0.2)	2 (0.2)
Musculoskeletal and connective tissue dis.	5 (0.5)	7 (0.5)
Neoplasms benign, malignant and unspec.	1 (0.1)	5 (0.4)
Nervous system disorder	93 (9.9)	130 (9.8)
Psychiatric disorders	15 (1.6)	26 (2.0)
Renal and urinary disorders	0	2 (0.2)
Respiratory, thoracic and mediastinal dis.	0	4 (0.3)
Skin & SC tissue disorders	1 (0.1)	10 (0.8)
Vascular	6 (0.6)	11 (0.8)

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 EP 6.29.1 and 6.29.2. Cases with incidence <0.1% are not included in this table. Patients with AE leading to early discontinuation by dose at onset are presented in the following table.

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The most common AE that led to discontinuation for "LCM total" in the EP S2 Pool were in the Nervous System disorders (9.1%), GI (2.6%), Eye (2.6%), General disorders and administration site conditions (1.8%) and Psychiatric disorders (1.7%).

AE leading to dropout in EP S2 by dose at the onset of the AE are presented in **Appendix 8.** The analysis shows that, 1%, 2%, 3%, 4%, 2%, 2%, and 0% developed a Nervous System disorder AE while receiving the 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day, 600 mg/day and >600 mg/day doses, respectively in the EP S2 Pool, with a suggestion of a dose response from 100 to 400 mg/day doses. However, when looking at discontinuations by modal dose (the most commonly received dose, data not shown), the incidence for the nervous system disorders was 28% for 100mg/day (i.e. 22 events among 79 patients who received 100 mg/day), 20% for 200 m/day, 1% for 300 mg/day, 8% for 400 mg/day, 7% for 500 mg/day, 4% for 600mg/day and 0 for >600 mg/day.

> *The study design hampers the interpretation of the open label data. It is unclear what the best way to look at these data is. Both approaches (modal and by dose at onset) involve confounding factors.*

Preferred terms for AE that led to discontinuation within the Nervous System disorders during the treatment phase in Pool S2 by dose at onset of the AE are presented in the following table.

Table 29. Lacosamide NDA. Incidence of treatment emergent AEs that led to early discontinuation in the Nervous System Disorders EP Pool S2 during the treatment phase by dose at onset of AE

MedDRA Nervous System Organ Class Preferred Term	LCM (mg/day)							
	100 (N=1323) n (%)	200 (N= 1297) n (%)	300 (N=1164 n (%)	400 (N=1076) n (%)	500 (N=675) n (%)	600 (N=525) n (%)	>600 (N=208) n (%)	Total N=1327 n (%)
Any	13 (1.0)	29 (2.2)	32 (2.7)	41 (3.8)	11 (1.6)	9 (1.7)	0	127 (9.6)
Dizziness	7 (0.5)	14 (1.1)	20 (1.7)	15 (1.4)	7 (1.0)	5 (1.0)	0	67 (5.0)
Coordination abnormal/clumsiness	4 (0.4)	2 (0.2)	4 (0.3)	8 (0.7)	1 (0.1)	1 (0.2)	0	20 (1.5)
Convulsion	3 (0.2)	6 (0.5)	2 (0.2)	4 (0.4)	0	1 (0.2)	0	15 (1.1)
Headache/ basilar migraine	1 (0.1)	2 (0.2)	3 (0.3)	4 (0.4)	0	0	0	9 (0.7)
Tremor	2 (0.2)	3 (0.3)	0	4 (0.4)	0	0	0	9 (0.7)
Balance disorder	1 (0.1)	0	3 (0.3)	4 (0.4)	0	0	0	8 (0.6)
Nystagmus	1(0.1)	1 (0.1)	1 (0.1)	2 (0.2)	0	1 (0.2)	0	6 (0.5)
Memory impairment	0	0	0	1 (0.1)	2 (0.2)	1 (0.2)	0	4 (0.3)
Status epilepticus	0	1 (0.1)	0	2 (0.20	0	0	0	4 (0.3)
Hipoaesthesia/paresthesia	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	5 (0.4)
Somnolence/sedation/lethargy	2 (0.2)	3 (0.3)	0	1 (0.1)	0	0	0	6 (0.5)
Cognitive disorder	0	0	0	1 (0.1)	0	1	0	3 (0.2)
Dysarthria/speech disorder	0	0	0	3 (0.3)	0	0	0	2 (0.2)
Subarachnoid hemorrhage	0	0	0	1 (0.3)	0	1 (0.2)	0	2 (0.2)
Disturbance in attention	0	2 (0.2)	0	0	0	01 (0.2)	0	2 (0.2)
Intracranial pressure increased	0	0	0	0	0	1	0	1 (0.1)
Mental impairment	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Amnesia	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Cerebellar syndrome	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Complex partial seizures	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Grand mal convulsion	1 (0.1)	0	0	0	0	0	0	1 (0.1)
Nervous system disorder	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Movement disorder	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Syncope	0	0	0	1 (0.1)	0	0	0	1 (0.1)

Source: Sponsor's Table EP.6.30.1 n = Number of subjects who reported at least one event during treatment. % = Percent with respect to the number of subjects for whom the dose was administered during treatment. Adverse events with a dose at onset of zero are not included in this table. 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.

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Dizziness was the mot common cause of discontinuation due to AE in EP Pool S2 (as well as EP S1), followed by ataxia (coordination abnormal). When looking at any seizure-related AE (including the PT convulsion, grand mal seizure, status epilepticus and complex partial seizures) by dose of onset in the S2 Pool (Table 29), the rates of discontinuation due to any seizure activity were as follows:

LCM 100 mg/d: 0.2% (4/1323)
LCM 200 mg/d: 0.5% (7/1297)
LCM 300 mg/d: 0.3% (3/1164)
LCM 400 mg/d: 0.6% (6/1076)
LCM 500 mg/d: 0 (0/525)
LCM 600 mg/d: 0.2 % (1/525)
LCM >600 mg/d: 0.5% (1/208)
LCM any dose: 1.6% (21/1327)

There is no evidence of a dose response for discontinuations due to seizure related AEs in the S2 Pool by dose at time of AE onset.

Review of datasets submitted on January 2008, as part of 120-day SUR indicates that a few more events leading to discontinuation occurred by the time of the cutoff date of June 2007, but the safety profile was consistent with the original submission.

- **AE leading to discontinuation in trials SP 586 and SP598 (oral capsule formulation)**

In SP586, no subject had a TEAE that led to discontinuation from the trial. Two subjects (Subject 3004, Subject 4001) withdrew early from SP598 due to AEs. The reported TEAEs were dizziness (moderate intensity; possibly related) and asthenia (mild intensity; possibly related). The dose at onset for both subjects was LCM 400mg/day.

- **AE leading to discontinuations in LCM IV studies**

  - Phase 1, single dose, IV LCM studies (4 studies)

In SP658, the events were mild nightmares/moderate anxiety, severe epiglottitis, and a moderate common cold. In SP643 one had an increase of QTc from Baseline ≥60ms 4 hours after the start of infusion during treatment with iv LCM 200mg. The narrative of the case from study SP 643 is as follows:

-Subject # 643-10020 was a 35 year old Caucasian male, who received 200 mg of IV LCM on the morning of 9/16/02. The subject had been previously identified as a CYP2C19 poor metabolizer; was a smoker for 18 years and smoked 5 cigarettes/day. The infusion started at 7:30 AM. Three baseline 12-lead ECGs were recorded pre-dose, with the following QTc readings: 412 ms, 362 ms and 376 ms (a median 376 ms, was used for comparison). The automated QTc readings following the infusion are presented below:

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	Screening 4/9/02	Pre-dose 4/16/02 Median	1 hour after starting	4 hours after starting	8 hours after starting	12 hour after starting
Heart rate (bpm)	42	52	58	74	66	56
PR (msec)	138	132	148	140	138	132
QT (msec)	454	446	416	398	402	422
QTc (B) (msec)	390	376	405	444[2]	423[3]	409[4]
RR (msec)	1336	1232	1054	802	*904*	1064

[1] Mean/median 383/376 msec. [2] change from mean baseline= 97 ms. [3] change from median/mean baseline QTc= 47 ms. [4] change from mean/median baseline QTc= 33 ms.

The subject did not report any AEs. No clinically relevant findings were observed in labs and vital signs during the trial period 1 and the safety follow up examination on 9/23/02. The subject was withdrawn from the study according to the protocol. However, the manual evaluation by a cardiologist after the end of the trial revealed that the increase in QTc from Baseline was <60ms.

> *As noted in this table, the patient had baseline sinus bradycardia, but during the infusion his HR increased to 78bpm, coincidentally with a prolongation of the QTc. Although the manual reading of the QTc prolongation was <60 msec, the exact value was not provided. According to the table above, the change was 54 ms.*

- IV LCM in phase 2/3 partial onset seizures studies

There were 2 subjects (both in the 15-minute infusion duration group) who experienced TEAEs that led to early discontinuation from SP757.

- **Subject 757-170106** discontinued the trial because of the SAE of bradycardia. Two cardiologists concluded that "This AE can be reasonably interpreted as sinus bradycardia with **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." The event is described in detail in the Serious AEs section of this review.

- **Subject 757-70111** discontinued prematurely due to ECG QT correct interval prolonged. She was a 35-year-old white female with a medical history of depression, diabetes mellitus and hypertension. She entered the DB SP755 trial on 25 Jan 2005 and was randomized to oral placebo. After completing 12 weeks she enrolled in the open-label SP774 trial, and began oral LCM 200 on 28 Jul 2005. She continued participation in the SP774 trial, and also enrolled in the open-label SP757 trial on 29 Mar 2006. At the time of enrollment in the SP757 trial, she had been on LCM 200 for 244 days. A per the CRF, at the time of the AE of electrocardiogram QT corrected interval prolonged (QTc =507 ms), the subject was receiving LCM IV infusion #7 (100 mg BID). ECG done at screening and before and after the first IV infusion (Mar 30, 2006 in the morning) were read as normal. The ECG before the second infusion (Mar 30, 2006 in the evening) was read as normal, but the ECG done at 7.5 min into the infusion and all ECGs thereafter were read as "abnormal, not clinically relevant." The exact nature of the abnormality is not stated in the CRF.

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At the 02 Apr 2006 pre-dose time point, her QTc(B) was 490 ms at 07:02. The LCM infusion began at 08:01 at a rate of 0.67mL/minute (min) to be administered over 15 minutes. Approximately 8 minutes into the infusion #7, on day #4, the subject's QTc(B) increased to 507ms. The infusion was stopped at 08:09 due to the AE. As per the narrative she had a blood pressure of 110/60mmHg and a heart rate of 82bpm at 08:09, and did not experience any clinically relevant symptoms. The AE was reported to be resolved approximately 2 hours later at 10:02 (see the following table of values). The subject withdrew from the SP757 trial and restarted her oral LCM (100mg) the evening of 02 Apr 2006. ECG measurements on day at screening and day#4 are presented in the following table.

QTcB, PR intervals, QRS intervals, and ECG findings for Subject 170111

Date	Visit/ Relative Day or Time point	LCM dose (mg/day)	QTc Bazett (ms)	PR interval (ms)	QRS interval (ms)	ECG findings
SP755 Double-Blind						
23 Mar 2005	Visit 3 (Baseline2) /1	0	436	206	92	Normal
SP757 Open-Label						
29 Mar 2006	Screening /-1	200 (oral)	416	230	92	Normal, 1st degree AV block, NCR
02 Apr 2006	Predose/4	200 (iv)	490	242	90	Abnormal, NCR
	am 7.5min		507	254	90	Abnormal, NCR
	am 120min		488	232	90	Abnormal, NCR
	End of trial		485	210	88	Abnormal, NCR

AV=atrioventricular; ECG=electrocardiogram; iv=intravenous; LCM=lacosamide; min=minutes; NCR=not clinically relevant; QTcB=QT interval using Bazett correction
Note: Relative day was date of evaluation relative to date of trial medication start.
Note: Time point was time relative to start of iv infusion.
Note: Baseline2 was defined as the average of the 3 predose Baseline Visit values for SP755.

Concomitant medications at the onset of the event included insulin; amiloride/ hydrochlorothiazide, piroxicam, citalopram, sulpiride, valproate sodium and lamotrigine. The investigator considered the AE to be possibly related to LCM.

This patient developed QTc prolongation during the IV infusion #7. The QTc at screening to SP757 was 416 ms. The patient had presented intermittent PR prolongation during the oral LCM study.

- **Phase 1 studies with the oral formulation**

A summary of the cases that lead to withdrawal with the phase 1 oral formulation studies is presented as follows:

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Table 30. Dropouts during phase 1 studies with LCM oral tablet

ID	Age/ gender	Preferred term	LCM dose at AE onset (mg/day)	Relationship as per investigator	outcome
836-18	32 M	First degree heart block (PR=240 ms)	LCM 400	probable	resolved
620-12837	73 M	Extrasystoles	0	Not related	unknown
620-16228	76 M	Dyspepsia, tremor, HTN	LCM 100	Unlikely, possible, unlikely	resolved
620-17917	76 M	Arrhythmia	0	Not assessable	resolved
602-8010	25 M	Urinary tract infection	LCM 400	Unlikely	resolved
618-8019	39 M	Erythematous rash	0	Not related	resolved
863-80011	40 M	T wave inversion	100	Possible	resolved
599-8024	39 F	Eosinophilia	0	Not related	unknown
599-8030	23 F	Infection	0	Not related	ongoing
640-82044	22 F	Syncope/Mallory Weiss syndrome	800	Not related	resolved
640-82088	19 F	Neck pain	800	Not related	resolved

- **Subject # 836**-18 started LCM 200 mg twice daily on — On — day 3-, prior to taking his morning dose, he had heart block of severe intensity. It resolved the same day about 4.5 hours later. He did not take further doses, however, he experienced 3 additional episodes on November 21, 23 and 24, and lasted 4.5, 2 and 15 hours, respectively. He did not receive any particular treatment. On November 23 he also experienced elevated ALT <2xULN. b(6)

Comment: this event might be related to LCM, although it resolved at Tmax and recurred when the drug should have been washed out.

- **Subject# 863-80011** was randomized to sequence A-B on 9/1/05. On 9/3/05 while on Treatment A in Treatment Period 1 (single dose omeprazole 40 mg, multiple dose LCM 100-300 mg, twice daily) he experienced T wave inversion. The ECG finding was not accompanied by subjective symptoms and occurred at irregular intervals. The subject was withdrawn from the trial at the sponsor's request, on 9/7/05. The AE was considered resolved at the safety follow up visit on 9/21/05.

Comment: the finding of intermittent T wave inversion in the ECG in a healthy volunteer appears related to LCM. The clinical significance of this change is unclear, but T wave inversion is sometimes a sign of ischemia.

In summary, the rate of AE leading to dropout in EP S1 was 17.1% on LCM and 4.9% on placebo. The analysis of these events by randomization dose suggests a strong dose response (28.6% dropped out from the LCM 600 randomization group, as compared to 17.2% in the LCM 400 group). The analysis by dose at onset of the AE also shows a dose response up to LCM 500. As discussed earlier, interpretation of dose response in this database is limited by the titration study design and by fewer patients exposed to LCM 600 mg/day. Half of the AE leading to dropout were in the Nervous System disorders SOC (18.6%) and were mostly due to dizziness

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and cerebellar disorders (ataxia, nystagmus, tremor and balance disorders), which have been previously identified in the LCM non-clinical studies and in clinical studies with other AEDs.

7.1.4 Other Search Strategies – Adverse events of interest.

Based on non-clinical and clinical trial data as well as safety considerations related to drug class, the sponsor pre-specified certain AEs as "other significant AEs". These AE were related to cardiac and ECG abnormalities, syncope, abnormal liver function, rash, seizure, memory impairment, suicidality and weight change.

7.1.4.1 Cardiac and potentially cardiac AEs

Because of the mechanism of action (interference with slow sodium channels) and the non-clinical findings, ECG evaluation was one of the pre-specified "other adverse events of interest" in the clinical program. The non-clinical findings are summarized from the sponsor's Cardiac Report as follows:

> 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 starting at concentrations which are achieved with the highest recommended dose in the clinic. 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 dogs and monkeys. These effects started at the time of maximal drug plasma levels (Tmax), ie, **2 to 5 minutes after IV application, at plasma levels found in humans after 300mg bid** (14.5 ± 1.7µg/mL) and were accompanied by an **increase in PR interval and QRS complex** duration (approximately 5% and 10%, respectively). At all doses tested a slight but statistically significant increase of heart rate (3-7%) was determined. The cardiodepressant effects, hemodynamic changes and cardiac conduction effects were dose related. **Atrial conduction was affected at lower doses than ventricular conduction.** At higher doses (15-45mg/kg) severe conduction disturbances such as **AV block, AV dissociation and nodal rhythm** were observed, with marked reductions in blood pressure and cardiac output.

Standard 12-lead ECGs were performed at protocol-specified time points during all clinical trials included in this application. For phase 2/3 studies ECGs were evaluated by independent blinded analyses by central ECG readers. Additional details about the timing of ECGs in each protocol are presented in section 7.1.9 of this review.

ECG abnormalities were evaluated by analyzing treatment emergent adverse events under the Investigations/ ECG investigations HLGT and the Cardiac disorders SOC, as well as ECG analyses in EP Pool S1 and S2.

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- ECG related treatment emergent AEs in the Investigations SOC in EP S1

A summary of AE under the MedDRA ECG Investigations HLT is presented below.

Table 31. Adverse events under MedDRA Investigations SOC, ECG investigations HLT

MedDRA PT involving ECG	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	**0 (0)**	**2 (0.7)**	**2 (0.4)**	**4 (0.7)**	**8 (0.9)**
ECG abnormal	0	1	0	0	1
ECG QT corrected interval prolonged	0	1	1	1	3
ECG QRS complex abnormal	0	0	0	1	1
ECG QRS complex prolonged	0	0	0	1	1
ECG T wave abnormal	0	0	0	1	1
ECG PR prolongation	0	0	1	0	1

Source: Reviewer's analysis. AE datasets.

The analysis of AE reported under the Investigations SOC/ ECG investigations HLT, reveals 8 cases involving ECG abnormalities in the EP Pool S1 (all on LCM) with an overall incidence of 0.9% for LCM (8/944) and 0% for placebo (0/364). A listing of these cases is presented below.

Table 32. Pool EP S1. PT terms under the HLT ECG investigation

ID	TrtGroup	age (years)	gender	AE term	Rel st day (Phase)	AE Dose[1] (mg/d)
667015022	400	45	F	QTC-change from baseline equals 60 ms	98 (Ma)	400
667015502	200	29	M	QTC change from baseline equals 60 ms	8 (T)	0
667017204	200	41	F	Abnormality in ECG **(SAE & dropout)**	29 (T)	0
754011401	600	45	M	Prolonged QTC interval **(Drug withdrawn because of protocol violation)***	1 (T)	100
754016020	600	49	M	Low QRS voltage (ALSO RBBB)	15 (T)	200
754017602	600	23	M	T wave (non-specific) abnormality per ECG (01-jun-05)	17 (T)	200
754018501	600	38	M	Elevated QRS complex 111 ms (ECG)	30 (T)	500
755106406	400	61	M	PR time prolongation **(SAE & dropout)**	1 (T)	100

Source: ISS AE dataset EP Pool S1. *Narrative/CRF not available among discontinuations due to AE; available under "other significant AE". [1] Dose at time of AE onset.

The mean and median dose taken among those who were taking LCM was 220 and 200 mg/day, respectively. Except for one case that occurred during maintenance (ID# 667015022) all other cases occurred during titration. Three cases required drug withdrawal and two were considered serious. All cases recovered.

Narratives of cases requiring discontinuation are as follows:

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- **Subject # 667017204** was a 41-year-old white female with a history of hypertension. She entered the trial on 23 Sep 2002 with partial seizures. The subject was randomized to LCM 200 on 18 Nov 2003. On 16 Dec 2002, she developed chest pain and "ECG abnormal". At that time, the subject was still on **placebo**. She was discontinued from the study on 06 Jan 2003. The chest pain was considered resolved on 17 Dec 2002. The abnormality in ECG was considered resolved on 06 Jan 2003.

  This event occurred while the patient was on placebo, therefore, it is not related to LCM use. The narrative and CRF are unclear as to the nature of the ECG abnormality. A copy of the ECG is not included.

- **Subject #754011401** was a 45 year old male with history of hypertension, diabetes mellitus, depression and obesity, randomized to LCM 600 on May 19, 2004. He discontinued because of a baseline pre-dose QTc prolongation. The narrative and CRF explain that the patient was randomized "in error", and that the QTc prolongation was not evident until final ECG reading, therefore, the reason for discontinuation for this patient was Protocol violation. The following values were taken from the ECG datasets:

	May 19 (Pre dose)	May 25 (Visit 4)	Change from baseline
HR	79	59	-20
PR	181	210*	38 (*First degree AV Block)
QTc (mean)	471	412	-58
QRS	164	155	-9
RR	762	1013	251

  In this patient, the "QTc prolongation" preceded use of LCM. Additionally, in May 25, the QTc had shortened by 58 ms from pre-dose values and that he had first degree AV block. No follow up on this patient has been provided.

- **Subject 755106406** was a 61-year-old white male with medical history of obesity, myocarditis, hypercholesterolemia, apnea, and sick sinus syndrome with a pacemaker in place. He was randomized to LCM 400 on 09 Mar 2005. On 09 Mar 2005, during the Baseline Visit of the Titration Phase, the subject experienced ECG PR prolongation (211-216ms). The subject received his trial medication and began taking it on schedule achieving the randomized maintenance dose of LCM 400 mg/day. On 06 April the investigator referred the subject to a cardiologist 2005 due to the PR interval value of 294ms and other ECG findings. The cardiologist recommended discontinuing the trial medication. The subject therefore withdrew from the trial and took his last dose of trial medication on 09 May 2005. The trial medication remained blinded. The subject did not experience any cardiac symptoms and no therapeutic measures were used to treat the AE. The investigator subsequently reported that the PR interval prolongation did not abate after withdrawal of trial medication, and had completely resolved on 31 Aug 2005 after the cardiologist had adjusted the level of the subject's pacemaker.

  In this patient with a history of sick sinus syndrome, mild PR prolongation preceded the use of LCM. PR prolongation worsened with LCM, and persisted after drug withdrawal. The event resolved after pacemaker adjustment. The role of LCM in triggering the need for pacemaker adjustment can not be ruled out.

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- TAES in the Cardiac Disorders SOC

As per the sponsor's analysis, the rate of cardiac disorders AEs was 2.4% for LCM and 1.4% for placebo. TEAEs in the Cardiac Disorders SOC in EP Pool S1 during the treatment phase, by randomization dose are presented in Table 33.

Table 33. TEAE under the Cardiac Disorders SOC during the treatment phase EP Pool S1

MedDRA System Organ Class Preferred Term	Placebo (N=364) n (%)	Lacosamide 200mg/day (N=270) n (%)	Lacosamide 400mg/day (N=471) n (%)	Lacosamide 600mg/day (N=203) n (%)	Lacosamide LCM Total (N=944) n (%)
CARDIAC DISORDERS	5 (1.4)	6 (2.2)	13 (2.8)	4 (2.0)	23 (2.4)
BUNDLE BRANCH BLOCK RIGHT	2 (0.5)	0	3 (0.6)	2 (1.0)	5 (0.5)
PALPITATIONS	0	1 (0.4)	2 (0.4)	1 (0.5)	4 (0.4)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	2 (0.7)	1 (0.2)	1 (0.5)	4 (0.4)
ANGINA PECTORIS	0	1 (0.4)	2 (0.4)	0	3 (0.3)
SINUS BRADYCARDIA	0	1 (0.4)	2 (0.4)	0	3 (0.3)
EXTRASYSTOLES	1 (0.3)	0	2 (0.4)	0	2 (0.2)
BUNDLE BRANCH BLOCK	1 (0.3)	0	1 (0.2)	0	1 (0.1)
TACHYCARDIA	0	0	1 (0.2)	0	1 (0.1)
CARDIOMYOPATHY	0	1 (0.4)	0	0	1 (0.1)
BRADYCARDIA	1 (0.3)	0	0	0	0
VENTRICULAR EXTRASYSTOLES	1 (0.3)	0	0	0	0

Source: Sponsor's Table EP 6.1.1. One patient may have more than one event.

The most common cardiac disorder in EP S1 was R bundle branch block (BBB) followed by first degree AV block and palpitations. Cases were considered to be mild or moderate. There were no cases of serious QT prolongation-related AEs such as TdP or ventricular fibrillation. The mean and median doses at the time of the AE, among those patients who were taking LCM was 312 and 400 mg/day, respectively.

A listing of patients with AE of the Cardiac Disorders SOC in EP Pool S1 is presented in the following table:

Table 34. Summary of AE under the Cardiac Disorders SOC in EP Pool S1

ID	TrtGroup	Age/ gender	PT	AE dose	ACTION	Outcome
667013510	Placebo	50 M	BBB BBB R	0	No dose change No dose change	No yet completely R R
667016803	Placebo	24 F	Bradycardia	0	no dose change	R
754014210	Placebo	26 M	BBB R	0	NA	R
754015007	Placebo	23 F	Ventr. extrasystoles	0	no dose change	R
755106405	Placebo	54 F	Extrasystoles	0	no dose change	R
667015803	**LCM 200**	32 M	Cardiomyopathy	0	**WITHDRAWN**	ongoing
667016802	LCM 200	47 F	Palpitations	200	no dose change	R

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ID	TrtGroup	Age/ gender	PT	AE dose	ACTION	Outcome
667016816	LCM 200	52 M	AV block first degree	100	NA	R
667016926	LCM 200	26 M	AV block first degree	200	no dose change	R
755104506	LCM 200	37 F	Angina pectoris	200	no dose change	R
755108402	LCM 200	25 F	Sinus bradycardia	200	no dose change	R
754015602	LCM 400	31 M	R BBB	400	no dose change	R
667010115	LCM 400	18 F	Angina pectoris	200	no dose change	R
667011508	LCM 400	45 M	BBB	200	no dose change	R
667018818	LCM 400	30 F	Palpitations	300	no dose change	R
754010503	LCM 400	37 M	R BBB	400	no dose change	R
754011001	LCM 400	35 M	Palpitations	400	no dose change	R
754012205	LCM 400	51 M	BBB	400	no dose change	R
754012205	LCM 400	51 M	Sinus bradycardia	400	no dose change	R
754014204	LCM 400	67 M	AV block first degree	100	NA	R
754015606	LCM 400	45 M	R BBB	400	no dose change	R
755106302	**LCM 400**	54 F	**Extrasystoles**	100	**WITHDRAWN**	Lost to FU
755108401	**LCM 400**	41 M	**Sinus bradycardia**	100	**WITHDRAWN**	R
755110411	LCM 400	39 F	Tachycardia	400	no dose change	R
755114306	LCM 400	52 F	Angina pectoris	400	no dose change	R
755122303	**LCM 400**	39 F	**Extrasystoles**	400	**WITHDRAWN**	R
667016805	LCM 600	59 F	R BBB	400	NA	R
667010102	LCM 600	37 M	Palpitations	500	no dose change	R
667017310	LCM 600	21 M	AV block first degree	500	no dose change	R
754015005	LCM 600	28 M	R BBB	600	no dose change	R
754016020	LCM 600	49 M	R BBB	200	no dose change	R

Source: AE datasets.

Narratives of cases that led to withdrawal in the ECG Investigations or Cardiac disorders are as follows:

- **Subject 667015803:** 32-year-old white male randomized to LCM. At the onset of the AE of cardiomyopathy, the subject was taking LCM 100 and had started that day. The subject was asymptomatic. The Screening Visit EGC and the randomization visit (pre-dose and 2 hour post-dose) ECGs, showed non-specific ST and T wave abnormality and possible anterior ischemia, which the investigator did not consider clinically significant. When the ECGs were received from the central ECG lab, the reader marked them as "clinically significant." The patient remained asymptomatic, but was referred to a cardiologist for evaluation. The cardiologist diagnosed hypokinesis, due to non-coronary cardiomyopathy. Trial medication was discontinued and the subject withdrew from the trial on 03 Nov 2003. The event was reported as ongoing. The AE was reported as a nonserious AE. The investigator considered the AE of cardiomyopathy to be not related to trial medication.

In this case, the ECG changes preceded the use of LCM.

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- **Subject 755106302** was a 54-year-old white female randomized to LCM 400 on 15 Dec 2004. At the baseline visit, the ECG showed **extrasystoles**, an event not considered clinically significant. The subject was randomized and took trial medication from 15 Dec 2004 to 21 Dec 2004. On 21 Dec 2004, the investigator stopped the trial medication at the request of the sponsor's cardiologist. The patient had been taking only placebo. The event was unresolved, and the subject was lost to follow up.

  This event occurred before starting LCM.

- **Subject 755108401** was a 41-year-old white male randomized to LCM 400 on 04 Jan 2005. At the time of the report of the AE the subject was taking LCM 100 and had been at this dose level for 9 days. In Jan 2005 (exact date undetermined), during the dose Titration Period, the subject experienced **sinus bradycardia** (47 bpm) in association with asthenia (from 67 bpm at screening and baseline). Drug was withdrawn on Jan 21, 2005. The sinus bradycardia completely resolved by April 19, 2005. Concomitant meds were topiramate and carbamazepine.

  This patient developed sinus bradycardia (probably symptomatic, because of the asthenia associated with it) while on LCM 100 mg/day. The event resolved after drug discontinuation, although, it is unclear how long the event lasted. This event may be possibly related to LCM. ECG is not available.

- **Subject 755122303** was a 39-year-old white female. Her medical history included sinus bradycardia and atrial flutter. She was randomized to LCM 400 on Dec 9, 2004. At the time of the AE (extrasystoles, bigeminy) the subject was taking LCM 400 mg and had been at this dose for 6 days. At screening (10/4/04) she did have sinus bradycardia of 49 bpm. At baseline before dose (12/9/04), her heart rate was 43 bpm, with a QTc (mean)= 370 msec. On 01/4/04 she was found to have alternating premature bygeminy, frequent premature systoles, **P waves absent, junctional rhythm**, bradycardia (as per ECG datasets QTc was 314 msec). Concomitant medications at the onset of the AE included levetiracetam and lamotrigine. The AE of extrasystoles was reported as a nonserious AE, probably related to trial medication.

  This patient, with a baseline sinus bradycardia, developed worsening bradycardia with absent P waves and junctional rhythm. She had a previous history of sinus bradycardia and atrial flutter. The relationship to LCM can not be ruled out.

Three cases of angina pectoris occurred in EP S1. They were three females, ages 18 to 52, at doses of LCM 200 (n=2) and LCM 400 (n=1). None of them was considered serious or led to dropout. All recovered without dose change. No cases of angina were reported on placebo.

Three cases of chest pain have been discussed under discontinuations due to General disorder and administration site conditions. There were 2 on placebo and one on LCM. The role of LCM in this case can not be ruled out.

The cases of syncope are discussed separately in 7.1.4.2.

The following table summarizes cardiac and potentially cardiac AEs in EP S1.

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Table 35. Summary of treatment emergent cardiac-related or potentially cardiac-related during EP S1, treatment phase.

Adverse event[a]/ MedDRA preferred term	Placebo N=364 n (%)	All LCM N=944 n (%)
Rhythm-Conduction		
Bradycardia	1 (0.3)	0
Sinus bradycardia	0	3 (0.3)
Tachycardia	0	1 (0.1)
Heart rate increased	0	2 (0.2)
ECG PR prolongation	0	1 (0.1)
Atrioventricular block first degree	0	4 (0.4)
QRS-ST-T wave		
Bundle branch block right	2 (0.5)	5 (0.5)
Bundle branch block	1 (0.3)	1 (0.1)
ECG QRS complex abnormal	0	1 (0.1)
ECG QRS complex prolonged	0	1 (0.1)
ECG QT corrected interval prolonged	0	3 (0.3)[b]
ECG T wave abnormal	0	1 (0.1)
Other		
Chest pain	4 (1.1)	14 (1.5)[b]
Chest discomfort	2 (0.5)	3 (0.3)[b]
Angina pectoris	0	3 (0.3)
Syncope	1 (0.3)	1 (0.1)
Loss of consciousness	0	1 (0.1)
Depressed level of consciousness	0	2 (0.2)
Palpitations	0	4 (0.4)
Ventricular extrasystoles	1 (0.3)	0
Extrasystoles	1 (0.3)	2 (0.2)
ECG abnormal	0	1 (0.1)[b]
Cardiomyopathy	0	1 (0.1)
Heart sounds abnormal	0	1 (0.1)

AE=adverse event; ECG=electrocardiogram; LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities. a AE terms are grouped by a SCHWARZ internal convention for ECG data.
b One of 3 subjects for whom the AE of QT corrected interval prolonged was reported (Subject SP667/15502), 2 of 14 subjects for whom the AE of chest pain was reported (Subject SP667/17301 and SP667/18501), 1 of 3 subjects for whom the AE of chest discomfort was reported(Subject SP667/11809), and the subject for whom the AE of ECG abnormal and chest pain was reported (Subject SP667/17204) were actually taking a 0mg daily dose of LCM (ie, placebo) at the time of each event. Source: page 134 of sponsor's Cardiac Report. [As per the datasets one patient on placebo had two separate events of BBB and BBB right; as per the narrative, the patient who developed cardiomyopathy had an abnormal ECG at screening, before taking LCM].

The percentage of patients with any cardiac-related or potentially cardiac related AEs estimated from the above table (accounting for patients who were taking placebo during the LCM titration period as exposed to placebo) is 5.0 % for LCM (47/944) and 2.3% (18/781) for placebo.

- Cardiac Disorders SOC and ECG investigations HLT in EP S2

TEAE in the Cardiac disorders SOC and ECG investigations HLT are presented below:

Table 36. TEAE in the Cardiac disorders SOC and ECG Investigations HLT in EP S1 and EP S2 (as per SUR)

	EP SP 1			EP SP 2
MedDRA SOC/PT	Placebo N=364 n(%)	LCM N=944 n(%)	MedDRA SOC/PT	LCM N=1327 n(%)
CARDIAC DISORDERS	5 (1.4)	23 (2.4)	CARDIAC DISORDERS	69 (5.2)
BUNDLE BRANCH BLOCK RIGHT	2 (0.5)	5 (0.5)	BUNDLE BRANCH BLOCK RIGHT	15 (1.1)
PALPITATIONS	0	4 (0.4)	PALPITATIONS	12 (0.9)
ATRIOVENTRICULAR BLOCK FIRST D	0	4 (0.4)	ATRIOVENTRICULAR BLOCK FIRST DEGREE	9 (0.7)
ANGINA PECTORIS	0	3 (0.3)	SINUS BRADYCARDIA	9 (0.7)
SINUS BRADYCARDIA	0	3 (0.3)	ANGINA PECTORIS	8 (0.6)
EXTRASYSTOLES	1 (0.3)	2 (0.2)	TACHYCARDIA	3 (0.2)
BUNDLE BRANCH BLOCK	1 (0.3)	1 (0.1)	BUNDLE BRANCH BLOCK	2 (0.2)
TACHYCARDIA	0	1 (0.1)	MYOCARDIAL INFARCTION	2 (0.2)
CARDIOMYOPATHY	0	1 (0.1)	SINUS TACHYCARDIA	2 (0.2)
BRADYCARDIA	1 (0.3)	0	ATRIAL FIBRILLATION	2 (0.2)
VENTRICULAR EXTRASYSTOLES	1 (0.3)	0	EXTRASYSTOLES	2 (0.2)
			CARDIOMYOPATHY	1 (<.1)
			CYANOSIS	1 (<.1)
			SUPRAVENTRICULAR EXTRASYSTOLES	1 (<.1)
			CARDIO-RESPIRATORY ARREST	1 (<.1)
			WOLFF-PARKINSON-WHITE SYNDROME	1 (<.1)
			ACUTE MYOCARDIAL INFARCTION	1 (<.1)
			CARDIAC ARREST	1 (<.1)
			VENTRICULAR EXTRASYSTOLES	1 (<.1)
			BUNDLE BRANCH BLOCK LEFT	1 (<.1)
			CARDIAC DISCOMFORT	1 (<.1)
			CARDIOVASCULAR DISORDER	1 (<.1)
ECG Investigations				
ECG QTc interval prolong	0	3 (0.3)	ECG QTc prolonged	5 (0.4)
ECG QRS complex abnorm	0	1 (0.1)	ECG QRS complex abno	1 (0.1)
ECG QRS complex prol.	0	1 (0.1)	ECG QRS complex prol.	4 (0.3)
ECG T wave abnormal	0	1 (0.1)	ECG T wave abnormal	1 (0.1)
ECG PR prolongation	0	1 (0.1)	ECG abnormal	3 (0.2)
ECG abnormal	0	1 (0.1)	ECG change	2 (0.2)

Source: Table EP 6.1.1 and EP 6.1.2 Safety Update Report.

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Forty-six patients had AE in the Cardiac disorders SOC and 8 patients had ECG investigations AEs during the open label phase of the epilepsy studies. These include five additional patients with first degree AV block, six additional patients with sinus bradycardia, 5 additional patients with QTc prolongation, five cases of angina pectoris and two myocardial infarctions. In the absence of a placebo control, these findings are difficult to interpret. Some of the patients in EP Pool S2 were exposed to LCM for up to five years.

Six patients discontinued during the open label phase of the studies because of cardiac or ECG related events at doses of LCM 250 to 400 mg daily. All but one were considered serious. Three resolved, two did not fully resolve and one was fatal. As summary of the cases is presented in the following table:

Table 37. Listing of patients who discontinued due to cardiac disorders or ECG investigations during the OL phase of epilepsy studies.

USUBJID	Age/ gender	AETERM	Serious	Outcome	Rel study day	LCM Dose (mg/d)
607001562	47 F	Complete right bundle branch block (on ECG)	Y	R	63	250
667010502	47 F	Increased QRS	Y	R	199	300
667016937	61 F	Prolonged QTc more than 60 ms.	N	R	807	400
754012317	27 F	Cardiopulmonary arrest	Y	fatal	275	400
755108404	30 F	Tachycardia	Y	recovering	183	300
755122402	36 M	Acute myocardial infarction	Y	recovering	572	300

Source: Reviewer's analysis. AE datasets. SUR.

The case of cardiorrespiratory arrest in subject# 754012317 has been described under Deaths.

The narrative of the case with R BBB who led to discontinuation is as follows:

- **Subject # 607001562** was a 47-year-old white female with no CV history. On 12 Dec 2001, during the Maintenance Period, the subject experienced **complete right bundle branch block [on EKG]).** The event was reported as completely resolved on 27 Dec 2001. Concomitant meds included dilantin and oxcarbamazepine. As per a note in the CRF, the patient had a prior history of incomplete RBBB, however, the baseline ECG was read as normal. On 10/17/01, the ECG before dosing was read as normal; 2-4 hours after dosing was read as abnormal not clinically significant. On 12/12/01, there was no ECG before dosing; the ECG after dosing was read as "abnormal, clinically significant". The investigator thought it was probably related to study therapy.

  This event of complete R BBB occurred in a patient with a reported prior history of incomplete RBBB but normal ECG at study entry. O day 63 of study therapy, 2 and-4 hours after dosing she had a complete R BBB. The ECG abnormality resolved. The event appears related to LCM.

b(4)

In summary, The percentage of patients with any cardiac-related or potentially cardiac related AEs (accounting for patients who were taking placebo during the LCM titration period as exposed to placebo) is 5.0 % for LCM (47/944) and 2.3% (18/781) for placebo. The difference is driven by a higher rate of rhythm and conduction disorders in the LCM treated group, mainly PR and QRS prolongation. There were 4 cases of first degree AV block in the LCM group (4/944= 4.2%) versus 0% on placebo. The numbers are small but consistent with the effects identified in the LCM non-clinical program as well as the ECG evaluations in the clinical program.

Three subjects taking LCM presented heart conduction disorders that led to dropout (two cases of bradycardia and one PR prolongation in a patient with sick sinus syndrome) in EP S1. There were no cases of second degree AV block or serious arrhythmias in the EP S1 or EP S2 database. Interpretation of the data from the long term exposure database is difficult to interpret because of the lack of a control arm.

- Cardiac events with the IV formulation

The IV LCM program includes four phase 1, single dose studies in healthy male volunteers (total of 86 subjects exposed to LCM) and two phase 2/3 studies in 199 patients with partial onset epilepsy who had previously been exposed to oral LCM in open label studies. Altogether there were 285 subjects exposed to LCM intravenous formulation.

In SP834 (single dose), there were 2 cardiac-related adverse events reported. Both were asymptomatic and occurred in the 300mg LCM group.

-**Subject 834-22** was a 22 year old male who developed a complete R BBB (QRS=120 ms) at the two hours post dose ECG. He had received LCM 300 mg intravenously. The event lasted 3 hours and 45 minutes. No concomitant medications were recorded for this subject. No therapeutic measures were taken to treat the event. ECG results for this subject are presented as follows:

Visit/Day	LCM Dose (mg/day)	Heart Rate[b] (bpm)	PR (ms)	QRS (ms)	QTc (ms)	Pertinent Morphologic Findings
Screen 28 Jul 1998	0	70	168	108	392	N/A
Screen Repeat	0	82	164	108	424[a]	N/A
Day 1/ Predose 17 Aug 1998	0	55	164	112	391	N/A
Day 1/ 1h Postdose	300	64	188	112	398	Right bundle branch block
Day 1/2h	300	62	160	120[a]	414	N/A
Day 1/24h 18 Aug 1998	300	63	188	112	402	N/A
Post-Trial 24 Aug 1998	0	70	168	116	413	N/A

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*This healthy subject had a **transient R BBB** 4 hours after initiation of the IV infusion. Since this was a single dose study, the patient did not dropout.*

-The second subject from the IV 300mg group developed a prolongation of PR interval from 176ms at Baseline to 212ms, 216ms, and 200ms on the 15min, 1hr, and 2hr post-dose ECGs, respectively. The PR interval had returned to 184ms on the 4hr post-dose ECG. No concomitant medications were recorded for this subject. No therapeutic measures were taken.

*This healthy subject had a **first degree AV block** (PR=216 ms, a 40 ms increase from baseline) 1 hour after initiation of the 300 mg IV infusion. Since this was a single dose study, the patient did not dropout.*

One subject in SP 645 had first degree AV block with the IV infusion, as follows:

- **Subject # 81002**, had first-degree AV block reported as an adverse event following IV administration but not following oral administration. Fifteen minutes after the start of IV infusion of LCM, the subject experienced a first-degree AV block with a PQ/PR value of 228ms (Baseline=204ms). Fifteen minutes later the PQ/PR had decreased to 216ms. Thirty minutes later the PQ/PR had decreased to 212ms. All subsequent PQ/PR measurements were <200ms.

*This healthy subject had **first degree AV block** 15 minutes into the IV infusion with a PR up to 228 ms, from 204 ms.*

In SP658 there were no subjects who experienced treatment-emergent cardiac-related adverse events. However, 2 subjects with pre-existing first-degree AV block were withdrawn following their first exposures (1-oral, 1-60min infusion) because their conditions were judged to be clinically relevant. Because both subjects had pre-existing AV block prior to LCM, neither case was reported as an adverse event.

- One SP658 subject (80012) had a first-degree AV block considered to be clinically relevant at the Eligibility assessment (EA) and all subsequent measurements. At the EA visit, the subject had a PQ/PR value of 228ms. In a repeat measurement the next day, the value was 206ms. The Baseline values prior to first administration of LCM (oral) was 246ms. At 1hr post-dose the PQ/PR was 260ms, at 4hr the PQ/PR was **276ms**, at 8hr the value was below Baseline (240ms). After completing Period 1, the subject was withdrawn from the trial due to his pre-existing clinically relevant AV block. At the Safety Follow-Up visit the subject's PQ/PR was 224ms.

-The second SP658 subject (81019) also experienced a first-degree AV block that was considered to be clinically relevant in all pre- and post-dose measurements on Day 1/Period 1. At the EA visit, the PQ/PR interval was 204ms. At Baseline the PQ/PR interval was 224ms. At 30 minutes, 1hr, 4 hrs, and 8 hr following completion of a 60min infusion the PQ/PR interval was **242ms**, 240ms, 238ms, and 212ms, respectively. At 24hr post-dose, a PQ/PR interval of 208ms was judged to be a "borderline PQ interval" by the investigator. The subject was withdrawn from trial at the request of the sponsor.

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*These two healthy subjects had a pre-existent first degree AV block (228 and 224 ms, respectively), and presented **worsening AV Block** (up to 276 and 242 ms, respectively) one after the oral tablet, one after LCM IV 60 min infusion. Since they had a pre-existent first degree AV block, they were not considered treatment emergent AEs, but they should have, as they represent worsening of a pre-existent condition, and first degree AV block was not a reason for exclusion.*

- IV LCM in epilepsy studies (total of 199 exposed to LCM)

Among the 60 subjects who participated in SP616 there was 1 treatment-emergent, cardiac-related adverse event reported.

- **Subject 10540**, a 35-year-old Caucasian male received oral LCM (300mg/day)/IV placebo (PBO) during Cohort A. At Baseline in the subject's original trial, he had a QRS measurement of 118ms; at Screening in SP616, the subject had a QRS of 128ms. The subject experienced an increase in QRS up to 134ms on Day 1. This was reported as an AE (Abnormal ECG) although there were no other associated adverse events. The AE was not serious, was mild in intensity, and was judged by the investigator to be unrelated to trial medication. This AE was not resolved as of database lock.

This patient had a prolonged QRS up to 134 ms. This represents only a 6 ms increase from baseline in SP616, but an 16 ms increase from the original QRS in the oral LCM study. The finding does not appear to be clinically relevant.

Serious AE and AE leading to dropout under the cardiac disorders SOC and ECG investigation disorders HLT in the IV LCM studies have been discussed in sections 7.1.2 and 7.1.3 of this review. There were three cardiac/ECG related dropouts among all patients exposed to the IV formulation. One was a case of QTc prolongation (close to 60 ms) 4 hours after the start of a single IV infusion in SP643. Another was a case of QTc prolongation up to 507ms, 8 minutes into infusion #7 (100 mg over 15 min) in SPS757 and the third was a case of bradycardia (26 bpm, sinus bradycardia with junctional escape vs. AV block with sinus exit block) also in SP757 (150 mg over 15 min) . I am particularly concerned about this case, because a sinus exit block is consistent with the known effects of higher doses of LCM and non-clinical studies.

In summary two subjects presented first degree AV block, one developed right BBB, two had QTc prolongation and one had profound bradycardia with a question of a sinus bradycardia or AV block with sinus exit block, with the IV formulation. Therefore, 1.8% of subjects with normal ECG at baseline developed AE of rhythm or conduction disorders with the LCM intravenous formulation (5/285) and 1.1% (3/285) discontinued the studies because of these events.

- Cardiac/ECG events in the DPN population

A detailed evaluation of the cardiac safety of LCM in the DPN population has been conducted by Dr. Pokrovnichka (DAARP). The following table has been taken from her review:

Table 38. Cardiac AEs for DPN controlled studies (Dr. Pokrovnichka's analysis; table 25 of her review)

SOC/PT	PBO	% PBO	200mg LCM	200%	400mg LCM	400%	600mg LCM	600%	LCM Total	% LCM Total
	N=291		N=234		N=426		N=363		N=1023	
	N	%	N	%	N	%	N	%	N	%
Cardiac-related events	**23**	**7.9**	**35**	**15.0**	**51**	**12.0**	**31**	**8.5**	**117**	**10.5**
Cardiac disorders	**14**	**4.8**	**14**	**6.0**	**30**	**7.0**	**22**	**6.1**	**66**	**6.5**
Palpitations	1	0.34	3	1.28	2	0.47	4	1.1	9	0.88
Tachycardia	0	0	1	0.43	5	1.17	0	0	6	0.59
Atrioventricular block first degree	0	0	1	0.43	2	0.47	2	0.55	5	0.49
Bradycardia	1	0.34	1	0.43	1	0.23	3	0.83	5	0.49
Bundle branch block left	4	1.37	2	0.85	2	0.47	1	0.28	5	0.49
Bundle branch block right	2	0.69	1	0.43	2	0.47	2	0.55	5	0.49
Angina pectoris	0	0	0	0	3	0.7	1	0.28	4	0.39
Angina unstable	0	0	0	0	4	0.94	0	0	4	0.39
Atrial fibrillation	0	0	1	0.43	0	0	3	0.83	4	0.39
Atrial flutter	0	0	1	0.43	1	0.23	1	0.28	3	0.29
Coronary artery disease	2	0.69	1	0.43	2	0.47	0	0	3	0.29
Myocardial ischaemia	1	0.34	1	0.43	0	0	1	0.28	2	0.2
Atrioventricular block second degree	0	0	0	0	1	0.23	0	0	1	0.1
Bradyarrhythmia	0	0	1	0.43	0	0	0	0	1	0.1
Cardiac arrest	0	0	0	0	0	0	1	0.28	1	0.1
Myocardial infarction	0	0	0	0	0	0	1	0.28	1	0.1
Nodal rhythm	0	0	0	0	1	0.23	0	0	1	0.1
Sinus bradycardia	0	0	0	0	1	0.23	0	0	1	0.1
Sinus tachycardia	0	0	0	0	1	0.23	0	0	1	0.1
Supraventricular extrasystoles	0	0	0	0	0	0	1	0.28	1	0.1
Supraventricular tachycardia	0	0	0	0	0	0	1	0.28	1	0.1
Ventricular fibrillation	0	0	0	0	1	0.23	0	0	1	0.1
Ventricular hypertrophy	0	0	0	0	1	0.23	0	0	1	0.1
Cardiac failure congestive	2	0.69	0	0	0	0	0	0	0	0
Ventricular extrasystoles	1	0.34	0	0	0	0	0	0	0	0
General disorders and administration site conditions	**5**	**1.7**	**12**	**5.1**	**7**	**1.6**	**5**	**1.4**	**24**	**2.3**

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SOC/PT	PBO	% PBO	200mg LCM	200%	400mg LCM	400%	600mg LCM	600%	LCM Total	% LCM Total
	N=291		N=234		N=426		N=363		N=1023	
	N	%	N	%	N	%	N	%	N	%
Chest pain	3	1.03	9	3.85	7	1.64	4	1.1	20	1.96
Chest discomfort	2	0.69	3	1.28	0	0	1	0.28	4	0.39
Investigations	**4**	**1.3**	**9**	**3.8**	**14**	**3.3**	**4**	**1.1**	**27**	**2.6**
SOC/PT	PBO	% PBO	200mg LCM	200%	400mg LCM	400%	600mg LCM	600%	LCM Total	% LCM Total
	N=291		N=234		N=426		N=363		N=1023	
	N	%	N	%	N	%	N	%	N	%
Electrocardiogram QT corrected interval prolonged	1	0.34	7	2.99	3	0.7	1	0.28	11	1.08
Electrocardiogram PR prolongation	0	0	0	0	4	0.94	0	0	4	0.39
Electrocardiogram abnormal	1	0.34	0	0	2	0.47	0	0	2	0.2
Electrocardiogram change	0	0	0	0	0	0	2	0.55	2	0.2
Heart rate increased	0	0	0	0	1	0.23	1	0.28	2	0.2
ECG P wave inverted	0	0	0	0	1	0.23	0	0	1	0.1
Electrocardiogram ST segment depression	0	0	0	0	1	0.23	0	0	1	0.1
Electrocardiogram ST-T segment abnormal	0	0	0	0	1	0.23	0	0	1	0.1
Electrocardiogram T wave abnormal	0	0	1	0.43	0	0	0	0	1	0.1
Heart rate irregular	0	0	1	0.43	0	0	0	0	1	0.1
QRS axis abnormal	0	0	0	0	1	0.23	0	0	1	0.1
ECG signs of MI	1	0.34	0	0	0	0	0	0	0	0
Pulse abnormal	1	0.34	0	0	0	0	0	0	0	0
(Source: Applicant's ae.xpt dateset from the iss)										

In DPN S1 there were 5 adverse events of first degree AV block (0.5%), 4 of atrial fibrillation, 3 of atrial flutter and one nodal rhythm, all in the LCM treatment group. No such cases were observed in the placebo treated group.

One patient reported intermittent second degree AV block but the finding was present before study entry:

- **Subject SP742/12308** was a 70-year-old male (assigned to the 400mg/day LCM group in SP742) who had second-degree AV block reported on his baseline ECG before study drug administration and ECG findings of 1st or 2nd degree AV block on ECGs at different visits. The subjects discontinued the trial due to other reason.

Additionally, one patient presented second degree AV block during the DNP open label studies (subject # 747/172706, a 59 year old female with prolonged PR at baseline who developed second degree AV block, bradycardia [HR=52 bpm] and bundle branch block while taking LCM 400) and one patient with painful postherpetic neuralgia was found to have second degree AV block during telemetry monitoring after a syncopal episode that occurred while on LCM 600, during the titration phase of the study (subject # 10097, discussed later, under 7.1.4.2). Both patients were withdrawn from the studies.

Summary of ECG and cardiac related events

In summary, the percentage of patients with any cardiac-related or potentially cardiac related AEs (accounting for patients who were taking placebo during the LCM titration period as exposed to placebo) is 5.0 % for LCM (47/944) and 2.3% (18/781) for placebo. The difference is driven by a higher rate of rhythm and conduction disorders in the LCM treated group, mainly PR and QRS prolongation. There were 4 cases of first degree AV block in the LCM group (4/944= 0.5%) versus 0% on placebo. In DPN S1 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 events appeared to be dose and concentration dependent. No evidence of QRS prolongation was observed in the DPN controlled database. Interpretation of the data from the long term exposure database is difficult because of the lack of a control arm. The numbers are small but consistent with the effects identified in the LCM non-clinical program.

In the IV studies, two subjects presented first degree AV block, one developed right BBB, two had QTc prolongation and one had profound bradycardia with a question of a sinus bradycardia versus AV block with sinus exit block, all with the IV formulation (rate: 5/285= 1.8%). Three of those patients dropped out because of these AEs (3/285= 1.1%). The rate of cardiac/ECG events in the IV and oral tablet databases can not be adequately compared because the database is too small for adequate safety comparisons.

To further evaluate the cardiac safety of lacosamide, consultation was requested from the Division of Cardio-Renal Products (DCRP). The consult was based on the review of the submitted QT/QTc study of lacosamide, protocol SP640 (described in detail in Section 7.1.10), and safety data from double-blind and open label safety trials for all populations studied. The DCRP's reviewer (Dr. Stephen Grant) concluded that:

- Lacosamide administration is associated with a dose/concentration dependent prolongation of the PR interval. This effect appears to be greater in older patients and patients with underlying cardiac disease, and may develop with prolonged lacosamide dosing.
- The increase in the PR interval 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 lacosamide is titrated to steady state in such patients.

- Myocardial ischemia may potentiate effect of LCM on the PR interval.
- Lacosamide's PR effect appears to resolve with drug discontinuation.
- Patients with diabetes and/or cardiovascular disease may be at increased risk of atrial fibrillation and/or flutter following treatment with lacosamide. (The data showed that only subjects administered LCM in the placebo controlled studies of diabetic neuropathy developed atrial fibrillation or flutter).

Syncope as a potential cardiovascular event is discussed in the following section.

7.1.4.2 Syncope

Syncope is a sudden and temporary loss of consciousness associated with a concurrent loss of postural tone, from which recovery is spontaneous and prompt. It is generally caused by an acute decrease in cerebral blood flow and may occur as a result of multiple etiologies, ranging from benign conditions such as orthostatic hypotension to life-threatening diseases such as arrhythmias and heart block. Because of the cardiovascular effects identified in non-clinical studies (heart conduction and hemodynamic effects), syncope was pre-defined as an adverse event of interest in this application. Of note, the terms syncope and loss of consciousness are coded under the MedDRA Nervous System disorders SOC.

Overall, as per the SUR, 38 subjects in the phase 2/3 studies (all indications) and four subjects in the phase 1 studies presented an episode of "syncope" or "loss of consciousness. Thirty six of the 38 were in patients taking LCM. Some of cases were interpreted by the sponsor as a vasovagal reaction or as having a neurologic cause (related to dizziness and ataxia). However, no ECGs were done at the time of or after these events in most cases. Based on the known effects of LCM in the heart conduction system and in the absence of a normal ECG at the time of these events, a LCM-related cardiac cause can not be ruled.

Patients who had syncope or loss of consciousness in EP S1 are presented in the following table.

Table 39. Listing of patients with loss of consciousness and syncope in EP Pool S1

ID	Age/ gender	Trt Group	PT	AE term/other terms	LCM dose	action	Outcome	Rel st day
667011 801	25 F	LCM 400	LOC (S)	LOC/dizziness, nausea, blurred vision, constipation	400	dose not changed	R	43
		LCM 400	LOC	LOC	0	withdrawn	R	51
667012 701	29 F	Placebo	Syncope	Syncope lasting 5-10 minutes	0	none	R	67
755106 201	41 M	LCM 200	Syncope	Syncope	200	none	R	113

Source: AE Database EP S1 submitted January, 2008. LOC= loss of consciousness. (S) Serious.
Rel day: relative day of study.

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Three patients presented syncope during the placebo-controlled phase (S1 pool). One patient was on placebo and two were receiving LCM (200 or 400 mg/day). One event was serious and required discontinuation (667011801, on LCM 400). The narrative of this patient is as follows:

- **Subject ID# 667011801** was a 25-year-old white female randomized to LCM 400 on 01 Jul 2002. At the time of the AE of chest pain, she was taking LCM 300 and had been at this level for 3 days. On 12 Aug 2002, during the last week of the Titration Phase, she experienced therapeutic response increased (fluctuating intoxication symptoms/"antiemetic drug effects") and syncope (loss of consciousness). At this time she was taking LCM 400 and had been on that level for 7 days. Concurrently, she was also experiencing intermittent lightheadedness and dizziness. Prior to the event, she had reported fatigue and serum sodium below the normal range. It was not recorded whether the syncope was witnessed or not. Systolic blood pressure was 8-12% lower than baseline during visits when subject was taking LCM; diastolic blood pressure was increased up to 3.5% above baseline during these same visits. She recovered completely on the same day of the AE; however, she withdrew from the trial. The tapering began on August 14 and treatment was discontinued on September 3, 2002. She reported a second syncopal episode while taking placebo in the Taper Phase (20 Aug 2002).The fatigue resolved on 11 Aug 2002. All episodes of dizziness were reported to be resolved by 3 Sep 2002. Concomitant medications at the time of the events included ibuprofen, levetiracetam and oxcarbazepine.

  No significant changes in ECG intervals were reported during the trial (see table below). However, no ECGs were done at the time of the events.

	7/1/02 Baseline (pre-dose, mean)	7/1/02 After dose	7/8/02	8/5/02	8/13/02	9/3/02 (taper week 2)
HR (bpm)	75	73	81	71	77	77
PR (ms)	138	124	144	128	134	124
QRS (ms)	100	94	102	98	100	98
QTc(B) (ms)	426	418	466	410	430	427
RR (ms)	805	822	741	845	779	779

Source: EP S1 ECG dataset.

This patient, with no previous cardiovascular history or episodes of syncope, developed syncope while on LCM 400. The syncope was preceded by several days of fatigue, lightheadedness, dizziness and low sodium. There is no mention of postural dizziness and were no measurements of orthostatic change, although a 8-12% decrease in BP is mentioned in the narrative. Apparently, there were no significant ECG changes (although they were not measured at the time of the syncopal episode). As per the narrative, the second syncopal episode occurred while the patient was on placebo, however, if the tapering was conducted as per protocol, 6 days into the tapering from LCM 400, the patient should still be on 100 or 200 mg of LCM. All events resolved after drug discontinuation. In my opinion this syncopal episode appears to be Lacosamide-related. The mechanism is unclear.

Cases of LOC and syncope that occurred during the open label extensions are presented below:

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Table 40. Additional cases of syncope during open label extension (EP S2)

ID	Age/ gender	AE term/other terms	LCM dose	action	outcome	Rel study day	Rel day OL
607001056	41 F	Syncope (during the visit)	600	none	R	57	57
607001201	41 M	Syncopal episode, he fell & (+) LOC ~30 sec	400	WITHDRAWN	R	27	27
607001101	31 M	Black outs	600	none	Ongoing	801	724
754012101	35 M	Syncopal spell (black out)	800	dose reduced	R	509	368
754015401	38 M	Blacked out	500	dose reduced	R	502	364
755110412	40 M	Syncope, intermittent	400	none	R	207	86
755116107	38 M	Series of syncope	600	dose reduced	R	275	148
755118805	54 F	Syncope	600	none	R	526	390

DB= Double blind. OL= open label. OLE= Open label extension. (S) Serious. Rel day: relative day of study. Rel day OL: relative day on LCM during the OL/OLE extension. [1] patient randomized to placebo.

As noted in this table, eight additional patients presented syncope during the open label phase/extensions at doses of 400 to 800 mg daily. One required withdrawal (607001201) and three required dose reduction. Most were mild to moderate in severity and recovered either with dose reduction (n=3), drug discontinuation (n=1) or without dose reduction (n=4). One patient did not recover and the black outs were still ongoing at the time of last follow up (this patient had not undergone dose reduction). The events of syncope appear to be dose related.

The narrative of the case that required withdrawal is as follows:

- **Subject ID# 607001201 w**as a 41-year-old white male. His medical history included depression. He began taking LCM 100 on 10 Oct 2001. At the time of the adverse events (AEs), the subject was taking LCM 400 and had been at this dose level for 5 days. On 05 Nov 2001, during the Titration Period, the subject experienced syncope, an accident not otherwise specified (NOS) (superficial abrasions to head secondary to fall), ataxia, diplopia and dizziness. It is unclear if he had more than one episode. ECG and vital signs by visit for patient 607001201 were as follows:

Visit/date	LCM dose mg/day	Heart Rate	PR interval (ms)	QRS (ms)	QTc (ms)	SDB/DBP (mmHg)
Screening 9/13/01	0	69	148	84	430	169/97
Titr. Wk1 10/10/01	0 / 100	70	156	92	?	144/88
Titr. Wk2 10/17/01[1]	100	80	156	92	448	165/96
Titr. Wk4 10/31/01[2]	100	92	156	92	458	148/92
End visit 11/15/01[3]	300 (?)	85	144	92	433	154/98

ECG automatic readings: [1] QRS duration abnormal, significant change in QTc compared with 9/13/01. Minimal criteria for anteroseptal infarct, new; interpretation unchanged from 10/10/01 probably due to lead placement. [2] left atrial enlargement; nonspecific T wave abnormality; abnormal ECG. [3] Non specific T wave abnormality, new. SBP=systolic blood pressure. DBP= diastolic blood pressure (SOURCE: CRF)

The subject discontinued trial medication because of the adverse event of syncope and lack of efficacy. He took his last dose on Nov 5, 2001. Concomitant medications at the onset of the events

Additionally, 13 patients in the LCM treatment group had the PT term "Positive Rombergism", under the Investigations SOC and 21 patients in the LCM treatment group had the PT "Gait disturbance", under the General disorders and administration site conditions SOC.
Except for one patient who had positive Rombergism as an isolated AE, these patients also reported AEs of ataxia, nystagmus, tremor, spasticity, dyskinesia, somnolence and/or dizziness.

The adverse events reviewed in Table 59 are consistent with the events observed in non-clinical studies (ataxia and tremor were observed in mice and dogs). These events are not unique to LCM. They are described with most marketed AEDs and were observed in the placebo (background AED therapy) group. Of note, while in animals CNS symptoms were reversible and no structural lesions were found, some of these AEs in clinical studies did not appear to recover by the end of the observation period. [redacted]

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2) Analyses of events consistent with Extrapyramidal Symptoms

Another PT that was very common within the Nervous System disorders SOC was "tremor." The PT tremor belongs to the MedDRA "Movement disorders (including parkinsonism)" HGLT. To evaluate whether tremor in this database was associated with extrapyramidal disorders, I did a search of the database using this HGLT.

Table 62. Treatment emergent AE in the Movement disorders, including parkinsonism HGLT in EP S1.

PT	N(Placebo) 364 n(%)	LCM all 944 n(%)
Patients with any PT under HGLT	22 (6%)	81 (8.6%)
Bradykinesia	0	1
Clumsiness	1	1
Dyskinesia	1	5
Hemiparesis	0	2
Hypokinesia	0	2
Intention tremor	0	5
Movement disorder	2	3
Psychomotor hyperactivity	0	1
Tremor	18	64

Source: AE EP S1 datasets (January 2008)

The difference between LCM and placebo in "Movement disorders (including parkinsonism)" HGLT is driven by the AE of tremor (n= 69 [7.3%] on LCM and 18 [5%] on placebo). Many of these were associated with cerebellar & coordination disorders. Regarding dyskinesia, there were 5 in the LCM group (0.5%) and 1 in the placebo group (0.3 %), however, one of the cases in the LCM group was before starting drug treatment. The AE terms reported by the investigator and

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coded to "dyskinesia" were jerkiness, intermittent jerking, muscle jerks in hands, arm jerking, limb jerking and similar terms. A listing of the cases of dyskinesia in EP S1 and EP S2 is presented in **Appendix 11.**

The mean and median dose of LCM at the time of onset of the dyskinesia was 459 mg/day and 500 mg/day, respectively (range 100 to 700 mg/day), which is higher than the mean/median dose for other AEs. They were mild to moderate in severity. None was serious or led to study discontinuation. The dose of LCM was unchanged in most cases (except one case that underwent dose reduction and one case in which LCM was interrupted). Most cases recovered without change in LCM dose. The duration of the dyskinesia was listed as one day to several months, and some events do not have the duration. Three cases were reported as not recovered at the time of last follow up.

Regarding other terms consistent with extrapyramidal symptoms, there were no cases of parkinsonism in the epilepsy population. However, one patient developed head tremor on LCM 100 mg/day, five developed hypokinesia (three during the double blind study, and two during the open label phase) at doses of 400 to 600 mg/day, and 2 had bradykinesia (one during the controlled phase, on day 113 on LCM 200 and one during the OL phase, on rel day 1211 on LCM 500). The patient who developed bradykinesia in the controlled phase was lost to follow up; the other patient recovered without dose change. No patients on placebo developed hypokinesia or bradykinesia.

> *COMMENT: Ataxia and nystagmus are common with all antiepileptic agents. Dyskinesia is listed as a infrequent AE (1/100 to 1/1000) in other AED labels. When looking at the investigator's term coded as dyskinesia, some of these terms could have also been coded as tremor or as a cerebellar and coordination disorder ("jerkiness, jerky movements"). At the FDA request, the sponsor submitted the narratives of all patients with dyskinesia. Unfortunately, the narratives do not add details or descriptions of the abnormal movements other than the AE terms. A review of the efficacy response in these patients and the seizure type they had at entry and at the time of the last evaluation, those jerky movements do not appear to be seizure activity. No particular concomitant medications were received by these patients at the time of the event.*

- Potential extrapyramidal symptoms in the DNP population

AE of dyskinesia and other potential extrapyramidal symptoms were not unique to the epilepsy population. An analysis of cases of dyskinesia in the DNP population found 4 cases, one during the placebo-controlled phase (on LCM 600) and three during the open label extension, at doses of LCM 300-600 mg/day. Additionally, four patients developed parkinsonism, one developed "dystonia" (AE term "orofacial dystonia"), and two developed "akathisia" (AE term: "arm restlessness" and "restless movements with hands") in the DNP database. There were no cases of hypokinesia or bradykinesia in the DNP database.

In summary, the rate of cerebellar and coordination disorders such as ataxia and nystagmus was higher in patients taking LCM as compared to placebo (background AED therapy). These are AE known to be associated with AEDs. There was no clear evidence of increased extrapyramidal symptoms.

3) Treatment emergent diseases and medications during the epilepsy studies

An analysis of treatment emergent diseases and treatment emergent medications during the epilepsy studies showed no major difference in the rate of treatment emergent diseases and medications between LCM and placebo in EP S1 (data not shown). The interpretation of data from EP S2 is difficult given the long-term exposure and the lack of a controlled arm. 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 (as per information submitted 5/21/08; data not shown). For many of the new diagnosis and new medications it is likely that the extended exposure period represented in EP Pool S2 would result in subjects being exposed to these medications as part of daily life and evolving standards of medical care.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Standard laboratory assessments were measured at protocol-specified time points during all clinical trials included in this application. Blood for routine hematology and serum chemistry testing was collected from all subjects at each visit. Urine specimens were collected for urinalysis at Visits 1,3, 6, and 9-12; Taper Visits 1 and 2; Transition Visits 1 and 2; and unscheduled visits. These analyses were performed by central laboratories. Laboratory parameters assessed in Phase 2/3 studies and laboratory values considered to be outside the normal range are presented in **Appendix 12.**

7.1.7.2 Standard analyses and explorations of laboratory data

1) Analyses focused on measures of central tendency

- EP S1 and EP S2

Across all LCM doses, all mean/median values for hematology parameters in EP Pool S1 and EP S2 remained within the normal range and were not different from placebo. The changes were similar to placebo and showed no suggestion of a dose-related change. There were no consistent trends or changes from Baseline for any hematology parameter likely to be related to therapy with LCM. Similarly, there were no clinically meaningful changes in hematologic parameters in

the studies with the oral capsule (SP586 and 598) and in the IV LCM trials. The median hematology parameters during the treatment phase in EP S1 is presented in **Appendix 13.**

In general, the point estimate for mean/median values for hepatobiliary tests in EP Pool S1 were similar or slightly higher for LCM as compared to placebo (with large Standard Deviations). They remained within the normal range and there was no evidence of a dose response. Mean ALT, AST, GGT and ALK phosphatase changes from baseline at different time points during EP S1 are presented in the following table.

Table 63. ALT (U/L) mean changes from baseline (±SD) EP Pool S1, by randomization dose.

	Placebo N= 364		**LCM 200 N= 270**		**LCM 400 N= 471**		**LCM 600 N= 203**	
	n	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**	**n**	**Mean (±SD)**
ALT (U/L)								
Baseline	364		270		471		203	
Change end Titration	340	-0.7 (9.3)	246	0.4 (17.2)	411	0.7 (13.8)	156	0.8 (7.6)
Change end of Mainten.	321	-1.0 (10.4)	220	-0.3 (13.2)	365	0.0 (9.6)	125	0.0 (6.4)
Change end of taper	30	-1.3 (6.4)	32	3.9 (27.1)	79	1.5 (14.6)	49	0.4 (9.4)
AST (U/L)								
Baseline	364		270		471		203	
Change end Titration	340	0 (8.7)	246	1.8 (20.6)	411	0.4 (8.1)	156	0.6 (4.7)
Change end of Mainten.	321	0 (5.5)	220	0.7 (7.7)	365	0.1 (6.1)	125	0.1 (5.0)
Change end of taper	30	0.2 (5.2)	32	1.8 (13.0)	79	0.6 (7.7)	49	0.3 (6.7)
GGT	340							
Baseline	364		270		471		203	
Change end Titration	341	-0.9 (17,3)	246	1.0 (19.2)	411	1.8 (15.8)	156	1.8 (14.4)
Change end of Mainten.	321	-0.7 (18.7)	218	1.6 (26.4)	365	2.0 (25.8)	125	2.4 (22.5)
Change end of taper	31	-1.9 (10.8)	32	3.4 (17.1)	78	2.3 (14.6)	49	3.0 (14.5)
ALK								
Baseline	364	-1.7	270		471		203	
Change end Titration	341	(13.10)	245	0.5 (11.2)	411	1.1 (13.8)	156	-0.2 (11.8)
Change end of Mainten.	321	-1.5 (14.8)	218	2.0 (16.3)	365	-0.8 (14.7)	125	- 0.7 (17.6)
Change end of taper	31	-0.7 (9.7)	32	2.8 (12.1)	78	-0.8 (15.6)	49	0.8 (11.4)

Source: Appendix 7.2.1, original submission. . ALT: alanine aminotransferase. AST: aspartate aminotransferase. GGT= gammaglutaryl transpeptidase. ALK= Alkaline phosphatase.

The mean/median values for other chemistry evaluations (electrolytes, BUN, creatinine, Calcium, chloride, bicarbonate, bilirubin, uric acid, glucose, cholesterol and triglycerides) remained normal and no different from placebo during EP S1. There were no consistent trends or changes from baseline in the median or mean clinical chemistry values during progressively increasing durations of exposure to LCM in EP S2 .(data not shown). In the phase 2/3 IV studies, in SP757 there was a mild increase in mean GGT (4 I/U) and glucose (up to 7.5 mg/dL) in the 15 min infusion group. No clear trends or notable findings were observed in urinalyses in all LCM studies.

2) Analyses focused on shifts from normal to abnormal, marked outliers and dropouts due to laboratory AEs.

The sponsor presented analyses of laboratory outliers, shifts from normal to abnormal and marked outliers and dropouts due to laboratory AEs. The following section summarizes the most relevant findings.

Hematology

- Analyses in EP S1

In EP Pool S1, the majority of subjects in all treatment groups had normal hematology values at Baseline and these remained normal during the Treatment Phase for all hematology parameters. Shift analysis of hematology parameters across time and LCM treatment groups revealed no clear trends or notable findings in EP S1, EP S2, oral capsule and IV LCM trials (data not shown). The rate of treatment emergent hematologic abnormalities in EP S1 is as follows.

Table 64. Incidence of treatment emergent marked hematology abnormalities, EP S1,treatment phase.

Laboratory parameter (unit)/criteria	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203	LCM Total N=944
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Hematocrit (%)					
≤0.85 LLN	5/354 (1.4)	2/266 (0.8)	5/466 (1.1)	4/200 (2.0)	11/932 (1.2)
≥1.15 ULN	1/355 (0.3)	0/267	0/468	0/201	0/936
Hemoglobin (g/L)					
≤0.85 LLN	5/354 (1.4)	1/265 (0.4)	3/466 (0.6)	2/199 (1.0)	6/930 (0.6)
≥1.15 ULN	1/355 (0.3)	0/267	0/468	0/201	0/936
WBC count (G/L)					
≤3.0	8/351 (2.3)	9/261 (3.4)	11/462 (2.4)	8/200 (4.0)	28/923 (3.0)
≥16.0	3/355 (0.8)	2/267 (0.7)	0/467	0/201	2/935 (0.2)

Source: Sponsor's table in page 520 of ISS

Of note the rate of leucopenia (WBC <3000 /L) in EP S1 was 4% in the LCM 600 mg group, as compared to 2.3% on placebo. However, neutropenia (granulocyte count <1500/L) was higher on placebo as compared to LCM (4.6%, 3.6%, 3.9%, 3.6% and 4.6% for placebo, LCM 200, LCM 400, and LCM 600, respectively, [data not shown]).

The percentage of patients with an eosinophil count ≥10% was slightly higher in the LCM treated group: Placebo= 1.7%, LCM 200= 2.7%, LCM 400=2%, LCM 600 2.5%, overall LCM = 2.3%, but this small difference is unlikely to be of clinical relevance. For all other cell types, the incidence of marked abnormalities with LCM was no different from or smaller than placebo.

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The most frequently reported TEAEs related to abnormal hematology values during the Treatment Phase in EP Pool S1 were neutropenia (1.1% for LCM total vs 1.1% for placebo), WBC count decreased (0.5% for LCM total vs 0.3% for placebo), and neutrophil count decreased (0.5% for LCM total vs 0.8% for placebo). No trends in the nature or frequency of hematology laboratory abnormalities reported as AEs were observed.

Four subjects (1 subject in the placebo group, 2 subjects in the LCM 200mg/day treatment group, and 1 subject in the LCM 400mg/day treatment group) were withdrawn from the double-blind, placebo-controlled trials in EP Pool S1 due to TEAEs related to abnormal hematology values, as follows: Subject 755102312 (placebo) was withdrawn due to a TEAE of neutrophil count decreased. Subjects 755112312 and 755118617 (both LCM 200mg/day) were withdrawn due to neutropenia. Subject 755116101 (LCM 400mg/day) was withdrawn due to a TEAE of thrombocytopenia (platelet count: 113G/L [normal range: 140G/L-450G/L]).

- Markedly abnormal hematologic parameters in EP S2

Markedly abnormal hematologic parameters in EP S2 are presented in **Appendix 14a.**

> *The rates of hematological abnormalities were slightly higher in EP S2 as compared to EP S1 particularly eosinophil count >10 % (overall LCM 2.5% in EP S1 and 3.6% in EP S2) and neutropenia <1500 /L (3.9 % in EP S1 and 6.2% in EPS2) but the interpretation is unclear in the absence of a control group.*
>
> *Of note, in EP S1 the rate of infections and infestations was similar for LCM (15.6%) and placebo (14.6 %). The rate in EP S2 was 35.6%. Serious infections and infestations were more frequent in the EP S2 pool as compared to the EP S1 pool too. This is not that surprising, given the longer exposure. The EP S2 pool includes patients exposed for several years and they were multiple concomitant medications that may have affected the WBC. The infections observed in these patients were common infections such as upper respiratory and urinary tract infections.*

- Markedly abnormal hematologic parameters with LCM IV infusion

In SP616 there were 3 cases of treatment emergent neutropenia with granulocyte count <1500 /L, all in the IV group (one on the 60 min infusion, 2 in the 30 min infusion), and none on placebo. In SP757 two patients developed neutropenia <1500/ L, both in the 15 min infusion. A table summarizing the incidence of treatment emergent marked hematology abnormalities during IV studies are presented in **Appendix 14.b.**

> *The rate of TE neutropenia < 1500 /L in SP616 is higher in the IV infusion treatment groups as compared with the oral LCM groups (3/39 =7.8%, vs 0/21). The numbers are small for definitive conclusions. In SP757, the rate of*

neutropenia is 2/160=1.3%, (similar to EP S1). Of note, several patients had baseline neutropenia <1500 /L in both SP616 and SP757, but is unclear whether they acquired it during EP S2 or before entering LCM. The clinical significance of this observation is unclear.

Chemistry:
Shift analysis of clinical chemistry parameters across time and LCM treatment groups revealed no clear trends or notable findings in EP S1, EP S2, oral capsule and IV LCM trials (data not shown). In general, shift analysis of LFTs across time among the LCM treatment groups revealed no clear trends or notable findings and were similar to placebo. No subject in any treatment group had a maximum total bilirubin value ≥2xULN during the Treatment Phase. Shift analyses for ALT and AST in EP S1 is presented in the following table.

Table 65. Shift from baseline to maximum value during treatment by multiple of ULN for LFTs in subjects with partial onset seizures (EP S1 and EP S2)

Parameter/treatment	Maximum Post-Baseline				
	<1xULN	1 to <2xULN	2 to <3xULN	≥3xULN	Missing
ALT					
Placebo (N=364)	306 (84.1)	47 (12.9)	3 (0.8)	0	8 (2.2)
LCM EP Pool S1 (N=944)	809 (85.7)	115 (12.2)	8 (0.9)	7 (0.7)	5 (0.5)
LCM Total EP Pool S2 (N=1327)	1052 (79.3)	235 (17.7)	20 (1.5)	11 (0.8)	9 (0.7)
AST					
Placebo (N=364)	336 (92.3)	17 (4.7)	1 (0.3)	2 (0.5)	8 (2.2)
LCM EP Pool S1 (N=944)	885 (93.8)	46 (4.9)	3 (0.3)	5 (0.5)	5 (0.5)
LCM Total EP Pool S2 (N=1327)	1200 (90.4)	105 (7.9)	4 (0.3)	9 (0.7)	9 (0.7)

Source: Sponsor table in page 512 of ISS. . ALT: alanine aminotransferase. AST: aspartate aminotransferase. LCM=Lacosamide. LFTs=liver function tests. ULN= upper limit of normal.

.In response to an FDA informational request, on 3/25/08 the sponsor provided an analysis of transaminase elevations x2 ULN in the EP S1 pool. This analysis showed that the rate of treatment-emergent transaminase elevation ≥2 x ULN during the placebo-controlled studies was
- For ALT: Placebo, 0.8%; LCM 200, 2.2%; LCM 400, 0.8%; LCM 600, 0.5%.
- For AST: Placebo, 0.8%; LCM 200, 1.1%, LCM 400 0.6%, LCM 600, 0%.
Therefore, there is a higher rate of ALT elevation ≥2 x ULN in the LCM group, but it does not appear to be dose related.

- Effect on cholesterol and triglyceride levels

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Increased cholesterol and TG levels were noted in non-clinical studies. There were no changes in mean and median cholesterol and TG levels in EP S1 or EP S2, over time. Since an analysis of an outlier analysis for TG levels was not included in the application, the FDA asked the sponsor to conduct such analysis in the placebo-controlled trials with epilepsy. As per information submitted on March 3 2008 (submission 0006) there is no clear effect of LCM on triglyceride levels in this population. There was a slightly higher rate of patients with an increase in TG of at least 1.5 xULN for LCM as compared to placebo, for the LCM 400 mg/day group, but not the 600 mg/day dose (**Appendix 15**), but the rate of patients with TG levels of at least 2xULN was lower for LCM as compared to placebo (data not shown). Therefore, there was no evidence that LCM significantly affected TG levels at therapeutic doses in this database.

- Markedly abnormal chemistries in phase 2/3 intravenous studies

The treatment groups are small for definitive conclusions about different safety for the oral vs. IV or for different infusion rates. In SP 616, two patients had TE increase in cholesterol >6.5 mmol/L (one after the IV infusion, one after oral tablet) and one had an increased chloride >112 mmol/L (after IV LCM). In SP757: there were two TE of low glucose (<50 mg/dL) and one of increased glucose >200mg/dL with the IV infusion. There was also one of each of the following: ALT>3xULN, GGT>x3 ULN, bicarbonate < 1.8, phosphorus < 2. Several patients had increased baseline cholesterol >6.5 mmol/L but it is unclear whether that was acquired during EPS2 or preceded the LCM treatment. Marked abnormalities in chemistries in phase 2/3 IV studies are presented in **Appendix 15.**

- Markedly abnormal chemistries in phase 1 oral formulation studies

A case of markedly elevated transaminases was described under serious AEs in phase 1 studies. This healthy volunteer developed hepatitis and nephritis 12 days after completed study SP588 at doses of LCM 400 mg bid. The bilirubin and prothrombin time (PT) were not available at the time of these AEs, therefore it is unknown whether the patient developed hepatic failure. This case was interpreted by the physicians who evaluated him as a delayed hypersensitivity reaction.

In summary: 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 effect in ALT and GGT. 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. Prothrombin time or other measurements of liver function were not evaluated in this clinical program.

The clinical significance of higher percentage of neutropenia in EP S2 as compared to EP S1 is unclear. Three cases of neutropenia occurred after single dose IV LCM (7.8%) as compared to none on the oral formulation (0/29). The clinical significance of this observation is unclear.

b(4)

7.1.8 Vital Signs

Standard vital sign measurements (systolic BP [SBP] and diastolic BP [DBP] and pulse rate) and body weight were measured at baseline and periodically at protocol-specified time points throughout the trials. Additional vital sign assessments were done in the thorough QT/QTc trial SP640 (TQTc) in which a systematic evaluation of the effect of LCM on vital sign measurements was done including an orthostatic assessments. No orthostatic measurements were taken in the phase 2/3 studies. Temperature was not measured in these studies.

7.1.8.1 Standard analyses and explorations of vital signs data

1) Analyses focused on measures of central tendencies

- EP S1, EP S2, IV infusions and healthy volunteers

In general, mean changes in BP and pulse rate were small across all LCM treatment groups, and were not different from placebo. There were no consistent trends or changes from baseline in median or mean vital sign values at the end of the controlled treatment period or during progressively increasing durations of exposure to LCM in EP S1 and EP S2 (measures of central tendency in EP S1 are presented in **Appendix 16.** There did not appear to be any clinically relevant abnormal findings in any vital sign measurement in the IV single and multiple dose IV LCM studies, except perhaps for the 10 min infusion in study SP757. In this study, mean SBP and DBP appeared to increase from baseline (day 1 pre-dose) in subsequent pre-dose infusions and increase further at 2 hours post infusion (see **Appendix 17**).

In the QTc study, there was a clear increase in mean SBP, DBP and pulse (SP640, the TQTc study with the oral tablet in normal volunteers) at the at the 800 m/day dose. A summary of mean changes from baseline in supine vital sign measurements in study SP640 is presented in the following table. The vital sign measurements on Day 3 and Day 6/End of Treatment were performed 2 to 3 hours after dosing, within the range that maximum plasma concentrations of LCM are expected.

b(4)

Table 66. Vital signs in study SP640 (day 6/end of study)

Summary of changes from Baseline in supine vital sign measurements (SP640 SS)

Parameter (unit) Time point	Placebo N=62			LCM 400mg/day N=60			LCM 800mg/day N=71		
	n	mean	SD	n	mean	SD	n	mean	SD
SBP (mmHg)									
Baseline	62	119.7	13.6	60	117.4	12.2	71	114.4	11.2
Day 6/End of Treatment	55	-2.5	9.8	57	1.9	8.6	56	8.6	9.7
DBP (mmHg)									
Baseline	62	64.3	8.1	60	63.7	7.0	71	62.4	7.0
Day 6/End of Treatment	55	2.0	6.5	57	3.9	7.2	56	10.3	7.4
Pulse rate (bpm)									
Baseline	62	66.8	9.3	60	66.3	9.3	71	67.1	8.9
Day 6/End of Treatment	55	-6.0	8.4	57	-1.0	6.5	56	2.7	10.1

bpm=beats per minute; DBP=diastolic blood pressure; LCM=lacosamide; mmHg=millimeters of mercury;SBP=systolic blood pressure; SD=standard deviation; SS=Safety Set. Source: Sponsor's table in pg. 244 of ISS.

As noted in this table, at the end of day 6 there was mild 2-4 mmHg increase in mean SBP and DBP in the LCM 400 group, with a more marked increase in the LCM 800 group (8.6 mmHg in SBP and 10.3 mmHg in DBP)

As mentioned above, study SP640 measured orthostatic changes (changes in SBP, DBP and pulse from supine to standing position) throughout the study. Orthostatic changes were defined as follows:

Change in	Notable	Highly notable
SBP (mmHg)	Decrease $\geq$ 20	Decrease $\geq$ 40
DBP (mmHg)	Decrease $\geq$ 10	Decrease $\geq$ 20
Pulse (bpm)	Decrease or decrease $\geq$ 15	Decrease or decrease $\geq$ 30

Source: page 104 of ISS.

A summary of orthostatic changes in Study SP640 is presented in the following table:

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Table 67. Summary of orthostatic change in vital signs in SP640 (Day 6/end of treatment) SS.

Parameter/ treatment group	Orthostatic change (supine to standing)			Change from Baseline		
	n	Mean	SD	n	Mean	SD
SBP (mmHg)						
+1 minute						
Placebo N=62	55	-0.9	10.3	55	-4.9	12.9
LCM 400mg/day N=60	57	1.6	9.8	57	-2.9	11.2
LCM 800mg/day N=71	54	2.6	9.6	54	-4.1	12.2
+3 minutes						
Placebo N=62	55	-1.3	9.3	55	-6.5	11.5
LCM 400mg/day N=60	57	2.6	10.6	57	-0.0	12.4
LCM 800mg/day N=71	54	2.3	11.6	54	-2.7	11.3
DBP (mmHg)						
+1 minute						
Placebo N=62	55	7.6	6.5	55	-3.9	8.0
LCM 400mg/day N=60	57	9.0	7.7	57	-2.0	8.6
LCM 800mg/day N=71	54	9.6	7.2	54	-1.8	8.3
+3 minutes						
Placebo N=62	55	7.9	7.8	55	-3.6	7.8
LCM 400mg/day N=60	57	10.2	6.3	57	-1.0	8.9
LCM 800mg/day N=71	54	10.4	7.4	54	-1.1	7.9
Pulse rate (bpm)						
+1 minute						
Placebo N=62	55	25.2	12.1	55	5.3	11.4
LCM 400mg/day N=60	57	23.5	11.3	57	5.5	13.8
LCM 800mg/day N=71	54	20.0	11.7	54	3.4	14.1
+3 minutes						
Placebo N=62	55	26.1	13.5	55	6.5	12.3
LCM 400mg/day N=60	57	23.3	11.3	57	3.3	13.7
LCM 800mg/day N=71	54	21.7	13.3	54	4.4	14.5

DBP=diastolic blood pressure; LCM = lacosamide; mmHg=millimeters of mercury; SBP=systolic blood pressure; SD=standard deviation; SS=Safety Set. Note: Vital sign measurements obtained during the Day -1 assessment at the +1 minute and +3 minute time points were considered Baseline. If there were multiple vital sign assessments prior to first dose, then the last assessment prior to first dose was used as Baseline. On Day 6, vital sign measurements were taken at +1 minute and +3 minute time points after standing. Source, pg 697 & 698 ISS.

As per this analysis, there was no evidence of orthostatic changes with LCM in SP640.

b(4)

2) Analyses focused on outliers, shifts from normal to abnormal and dropouts due to vital sign AEs.

Individual subject changes in vital sign measurements were analyzed using 2 different sets of criteria denoted as "abnormal" and "markedly abnormal as follows:

Table 68. Abnormal and markedly abnormal vital sign parameters in LCM studies

Vital sign parameter	Abnormal criteria
Pulse rate (bpm)	increase of ≥15 from Baseline decrease of ≥15 from Baseline increase of ≥30 from Baseline decrease of ≥30 from Baseline
SBP (mmHg)	increase of ≥20 from Baseline decrease of ≥20 from Baseline increase of ≥40 from Baseline decrease of ≥40 from Baseline
DBP (mmHg)	increase of ≥10 from Baseline decrease of ≥10 from Baseline increase of ≥20 from Baseline decrease of ≥20 from Baseline

Vital sign parameter	Markedly abnormal criteria
Pulse rate (bpm)	≥120 and increase of ≥15 ≤50 and decrease of ≥15
SBP (mmHg)	≥180 and increase of ≥20 ≤90 and decrease of ≥20
DBP (mmHg)	≥105 and increase of ≥15 ≤50 and decrease of ≥15

Source: Sponsor's ISS.

The criteria used by the sponsor to define outliers appears adequate.

In general, the number and percentage of subjects with an abnormal vital sign change from baseline at any visit during the Treatment Phase for EP Pool S1 were similar between LCM and placebo. Most cases occurred only once during treatment. See Table 67.

Table 69. Summary of subjects with post-Baseline abnormal and markedly abnormal vital sign measurements at any visit during the Treatment Phase (EP Pool S1)

Parameter Change Criteria	Placebo (N=364) n (%)	Lacosamide 200mg/day (N=270) n (%)	Lacosamide 400mg/day (N=471) n (%)	Lacosamide 600mg/day (N=203) n (%)
Systolic Blood Pressure (mmHg)	360	268	470	203
Increase >=20 mmHg	81 (22.5)	56 (20.9)	107 (22.8)	59 (29.1)
Increase >=40 mmHg	6 (1.7)	1 (0.4)	6 (1.3)	3 (1.5)
Decrease >=20 mmHg	66 (18.3)	57 (21.3)	65 (13.8)	39 (19.2)
Decrease >=40 mmHg	3 (0.8)	2 (0.7)	5 (1.1)	4 (2.0)
Diastolic Blood Pressure (mmHg)	360	268	470	203
Increase >=10 mmHg	141 (39.2)	119 (44.4)	202 (43.0)	99 (48.8)
Increase >=20 mmHg	28 (7.8)	19 (7.1)	38 (8.1)	25 (12.3)
Decrease >=10 mmHg	159 (44.2)	120 (44.8)	168 (35.7)	74 (36.5)
Decrease >=20 mmHg	21 (5.8)	17 (6.3)	31 (6.6)	14 (6.9)
Pulse Rate (bpm)	360	268	470	203
Increase >=15 bpm	77 (21.4)	62 (23.1)	104 (22.1)	51 (25.1)
Increase >=30 bpm	7 (1.9)	9 (3.4)	7 (1.5)	5 (2.5)
Decrease >=15 bpm	55 (15.3)	37 (13.8)	62 (13.2)	32 (15.8)
Decrease >=30 bpm	2 (0.6)	0	8 (1.7)	3 (1.5)

bpm=beats per minute; DBP=diastolic blood pressure; LCM=lacosamide; mmHg=millimeters of mercury; SBP=systolic blood pressure. Note: n for each parameter is the number of subjects with at least one evaluable change from Baseline assessment and is the denominator for the percentages. All reported values (including unscheduled visits) during the Treatment Phase are used to determine the change criteria. ubjects are counted once during the Treatment Phase regardless of the number of times achieving the change criteria. Baseline = last non-missing value prior to or at randomization during the double-blind trial. Source Sponsor's Appendix 9.4.1. ISS.

- Vital sign outliers/marked outliers in EP S2

In general, the incidence of post-Baseline abnormal and markedly abnormal vital sign measurements in EP Pool S2 was low and comparable to EP Pool S1 and placebo. For markedly increased or decreased SBP, DBP and pulse the overall rate was 1-2 % with no clear dose response or increased risk over time (data not shown).

- Vital sign outliers/marked outliers in IV LCM studies

No subjects met the criteria for markedly abnormal vital sign measurements in the single dose phase 1 IV infusion studies in healthy volunteers.

In study SP616, (single dose in patients with epilepsy), 1 subject receiving oral LCM and 1 subject receiving IV LCM in the 60-minute infusion duration group, each had one markedly abnormal low DBP value. In the IV LCM 30-minute infusion duration group, 1 subject had 1 low SBP, 1 subject had 1 low DBP, and 4 subjects had an abnormal high heart rate including one

with markedly abnormal heart rate of 128bpm on Day 1 pm at the 10-minute time point. No subject met the criteria of a heart rate ≤50bpm and a decrease ≥15bpm. The study was not powered or designed to allow safety comparisons.

In SP757, there were 16 subjects with marked outlier vital signs. One was in the 30-minute infusion (1/40= 2.5%) and 15 were in the 15-minute infusion group (15/100= 15%). Of those in the 15 min infusion, 10 were related to low blood pressure and 5 were related to high blood pressure. Again, the study design does not allow adequate safety comparisons between infusion rates. See Table below.

Table 70 Vital sign outliers in study SP 757

Infusion Duration (Cohort)	Parameter: Abnormal Value	Site Number / Subject Number
30-minute (Cohort A1)	Systolic BP: <=90mmHg and decrease of >=20mmHg	400/140002
15-minute (Cohort B1)	Systolic BP: <=90mmHg and decrease of >=20mmHg	308/130806, 401/140115
	Diastolic BP: <=50mmHg and decrease of >=15mmHg	308/130806, 500/150004
	Diastolic BP: >=105mmHg and increase of >=15mmHg	500/150009, 500/150010
15-minute (Cohort B2)	Systolic BP: <=90mmHg and decrease of >=20mmHg	322/132201, 400/140019, 600/160001, 701/170107, 701/170110, 701/170111
	Systolic BP: >=160mmHg and increase of >=20mmHg	701/170104
	Diastolic BP: <=50mmHg and decrease of >=15mmHg	300/130006, 701/170110
	Diastolic BP: >=105mmHg and increase of >=15mmHg	600/160003, 701/170102

Note: Baseline is defined as the assessment taken prior to the start of infusion on the morning of Day 1. Source: Appendix 13.3.

The sponsor concluded that the vital sign profile (SBP, DBP and heart rate) of oral LCM was similar to the intravenous infusion and that different infusion rates have no effects on vital signs. I can not agree or disagree with the sponsor because the IV studies were not designed to adequately address safety comparisons.

- Outliers/ marked outliers for Vital signs in SP640 (TQTc study).

Outlier analyses in SP640 do not suggest any particular trend for vital sign changes.

- Weight in epilepsy studies

In EP S1, there were no dose-related trends in mean changes in body weight across LCM treatment groups. Mean changes by dose are shown in **Appendix 18**. In EP S2, 10% of subjects had an increase in body weight of at least 10% during treatment and 8.0% of subjects had a decrease in body weight of at least 10% during treatment. Most changes in weight occurred during an open-label extension trial. Therefore, there was no particular pattern for weight changes with LCM.

> In summary: Evaluation of vital signs suggests that there is little or no effect on vital signs (SBP, DBP, heart rate, and weight), with therapeutic doses of LCM oral tablet in the epilepsy population. Orthostatic changes were not measured in phase 2/3 studies, but they were measured in SP640, the TQTc study in healthy volunteers. There was no evidence of orthostatic hypotension in this study, at doses up to 800 mg daily.
>
> Oral LCM 800 m/day in SP640 and IV LCM, 10-minute infusion in SP757 were associated with a mean increases in SBP and DBP (8-10 mmHg, on day 6 for SP 640 and 3-9 mmHg post dose, on day 2 in SP757 [other days were not provided]).
>
> In SP757, 10% of patients receiving the 15-minute infusion and 2.5% of those receiving the 30-minute infusion presented at least one measurement of marked hypotension (SBP < 90 and drop $\geq$ 20mmHg or DBP <50 and drop $\geq$ 15 mmHg). The study design does not allow adequate safety comparisons. There was no measurement of orthostatic changes in these studies.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Extensive ECG testing took place during the development of LCM. In vitro investigations of the CV 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 was associated with an increase in PR interval and QRS complex duration in anesthetized instrumented dog. No QT prolongation was observed in non-clinical database.

Standard 12-lead ECGs were performed at protocol-specified time points during all clinical trials included in this application. Cardiac safety evaluations included serial ECGs in each subject as

well as AE reports. ECGs were evaluated by independent blinded analyses by central ECG readers. ECG monitoring was slightly different for different studies. Specific monitoring in different protocols is presented in **Appendix 19.**

Overall, it appears that the ECG testing during the program was appropriate in this development program. Of note, however, when collected at protocol specified times of 2-4 hours post-dose, the Cmax may have been missed since the Tmax is reportedly 0.5-4 hours.

7.1.9.2 ECG analyses

The sponsor conducted analyses of standard measures of central tendency, outlier analyses and analyses of ECG morphology.

7.1.9.3 Selection of studies and analyses for overall drug-control comparisons

ECG evaluations were analyzed for different pools:

- Placebo-controlled trials in epilepsy (Pool S1)
- All studies in epilepsy (Pool S2)
- Studies with IV formulation
- Through QTc study in Healthy volunteers

1) Analyses focused on measures of central tendency

- Measures of central tendency in EP S1

There were no notable differences in ECG parameters across treatment groups at Baseline for EP Pool S1. Overall, LCM did not affect heart rate over time for EP Pool S1. Mean changes in heart rate showed a minimal increase at the end of the Titration Phase (1-3 bpm) and were no different at the end of the Maintenance Phase.

There was a dose-related increase in mean PR interval change from Baseline among the LCM treatment groups in EP Pool S1. The mean change from Baseline in PR interval at the end of the Maintenance Phase for **placebo, LCM 200, LCM 400, and LCM 600 was 0.3ms, 1.4ms, 4.4ms, and 6.6ms, respectively**. The mean maximum change variable is the maximum increase in PR interval observed anytime during the Treatment Phase. Subtraction of the placebo mean from LCM shows a increase of 1.5ms, 3.1ms, and 4.5ms in the LCM 200mg/day, 400mg/day, and 600mg/day groups, respectively. The PR did not seem to be affected by gender or by baseline PR or QRS duration. Concomitant use of lamotrigine and carbamazepine, two drugs known to cause some PR prolongation had a small or no effect on the PR prolongation associated with LCM alone (measured at the end of the maintenance period). (data not shown). An outlier analysis of PR prolongation showed that age >60 at baseline increased the risk of developing PR >220msec. All subjects with PR =>250 ms were in the 60-70 age category.

There was no apparent effect on QRS duration at LCM doses up to 400mg/day. **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**. Subtraction of the placebo mean from LCM for the mean maximum increase also shows essentially no effect on QRS duration with the resultant differences from placebo being -0.9ms, 0.5ms, and 0.4ms in the LCM 200mg/day, 400mg/day and 600mg/day groups, respectively. This small increase in QRS is unlikely to be of clinical significance.

Changes from Baseline in PR interval and QRS duration and time points are summarized in the following table.

Table 71. Changes from baseline in PR interval and QRS duration in EP Pool S1

Parameter/ time point	Placebo N=364			LCM 200mg/day N=270			LCM 400mg/day N=471			LCM 600mg/day N=203		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
PR interval (ms)												
Baseline[a]	360	160.6	22.09	267	158.5	20.86	465	158.8	21.93	203	155.9	19.24
Change End of TP	338	-1.1	13.76	246	2.1	13.24	405	4.2	13.70	154	5.4	11.83
Change End of MP[b]	322	-0.3	13.51	219	1.4	13.52	362	4.4	13.62	126	6.6	13.02
Min change Post-Baseline[c]	353	-13.2	11.38	265	-11.2	12.22	464	-8.6	12.00	202	-8.0	11.12
Max change Post-Baseline[c]	353	11.2	12.18	265	12.7	11.11	464	14.3	13.53	202	15.7	11.80
QRS duration (ms)												
Baseline[a]	361	93.0	10.50	267	93.1	10.12	465	93.4	10.36	203	92.5	11.15
Change End of TP	339	-0.8	7.95	246	0.0	8.06	406	1.1	8.09	154	1.7	7.59
Change End of MP[b]	323	0.0	7.71	219	-0.2	8.81	363	0.4	8.61	126	2.3	8.61
Min change Post-Baseline[c]	354	-7.6	7.36	265	-7.3	7.33	464	-7.4	8.33	202	-5.7	7.23
Max change Post-Baseline[c]	354	6.8	6.50	265	5.9	6.85	464	7.3	6.95	202	7.2	6.40

Source: Sponsor's table in pg 273 of ISS.
bpm=beats per minute; ECG=electrocardiogram; LCM=lacosamide; max=maximum; min=minimum; MP=Maintenance Phase; ms=milliseconds; SD=standard deviation; TP=Titration Phase
a The Baseline is the average of all predose measurements at Visit 3 during the double-blind trial.
b End of MP=Maintenance Month 3.
c Min (Max) change Post-Baseline=Minimum (maximum) of all reported values (including unscheduled visits) during the Treatment Phase.

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. A summary of the changes in QTc (B) in EP S1 is presented in the following table.

Table 72. Mean changes from baseline in QTc (B) (ms) in EP Pool S1

QTc (Bazett) (ms)	Placebo N= 364		LCM 200 N= 270		LCM 400 N= 471		LCM 600 N= 203	
	n	Mean (±SD)	n	Mean (±SD)	n	Mean (±SD)	n	Mean (±SD)
Baseline	339		267		465		203	
Change end Titration	323	-0.7 (16.3)	248	1.1 (16.2)	409	-0.1 (16.3)	154	1.8 (14.0)
Change end of Maintenance	323	-0.6 (15.1)	219	-0.2 (16.6)	366	-0.9 (16.8)	126	0.0 (13.6)
Change end of taper	30	1.9 (19.3)	32	3.1 (16.2)	79	1.2 (17.2)	48	-1.4 (15.0)

Source: Table EP.8.1.1 (12 Lead ECG by Timepoint in EP S1).

- Measures of central tendency in EP Pool S2

In EP S2, overall, LCM did not affect heart rate, QRS or QTc over time. There was a small increase in mean PR interval change from Baseline across all LCM modal doses for EP Pool S2 (4.5ms, 6.1ms, and 8.6ms at the end of 6 months, 12 months, and 24 months, respectively, for all modal LCM doses combined). The mean maximum change for LCM Pool S2 was 19.8ms. Interpretation of the ECG data over time was limited by the progressively decreasing number of subjects at the later time point.

- Measures of central tendency with the IV LCM infusion

  - Single-dose Phase 1 iv LCM trials in healthy subjects

In total, 85 healthy subjects across the 4 Phase 1 IV trials received IV LCM. Most subjects received a single dose of IV LCM 200mg, except in SP834, where subjects received a single dose of IV LCM 50, 100, 150, or 300, and 4 received placebo). In SP658, compared with mean Baseline values, the mean PR interval increased slightly after treatment with IV LCM. After IV administration in Treatment A (200mg over 30 minutes) mean PR increased by a maximum of 7.9 msec and after Treatment B (200mg over 60 minutes), mean PR values increased by a maximum 3.4 msec, respectively, 30 minutes after the initiation of infusion. In the subsequent measurements, the PR interval decreased. In SP643, SP645, and SP834 there was no evidence for PR prolongation.

  - IV LCM in partial-onset seizures

SP616: In this in-patient trial, subjects who had been taking LCM chronically were randomized (2:1) to receive twice daily LCM (200-600mg/day) intravenously (n= 39) or orally (n=21) for two days. There was no placebo in this study. Two analyses were conducted for PR duration: changes from Baseline1 (ECG prior to first IV LCM administration) and changes from Baseline2 (Baseline ECG from subject's original trial). Again, a small increase in mean PR interval was

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observed with LCM. Table 71 summarizes mean and median changes from baseline in PR interval by treatment group.

Table 73. Changes from baseline in PR interval (ms) in SP616 (LCM oral vs. IV)

Summary of changes from Baseline1 in PR interval (ms) on Day 2 am by time point (SP616 SS)

LCM infusion duration	Time point[a]	Day 2 am					
		oral LCM/ iv PBO			iv LCM/ oral PBO		
		n	mean (SD)	median[range]	n	mean (SD)	median[range]
60-minute	Predose	10	-1.8 (8.35)	0.0 [-18, 10]	19	0.4 (12.14)	0.0 [-26, 28]
	15min	10	3.0 (11.60)	1.0 [-8, 28]	19	8.8 (13.96)	10.0 [-30, 30]
	30min	10	3.4 (12.37)	3.0 [-12, 30]	19	6.7 (12.53)	4.0 [-18, 26]
	45min	10	2.4 (10.70)	5.0 [-12, 18]	19	10.2 (13.05)	14.0 [-18, 32]
	60min	10	2.2 (9.82)	2.0 [-12, 16]	19	5.7 (15.10)	6.0 [-28, 32]
	120min	10	0.4 (7.93)	-2.0 [-12, 14]	19	1.2 (13.49)	0.0 [-30, 22]
30-minute	Predose	11	0.2 (9.78)	2.0 [-22, 12]	19	4.0 (14.33)	0.0 [-18, 44]
	10min	11	0.7 (9.48)	2.0 [-14, 20]	18	8.7 (9.25)	10.0 [-8, 20]
	20min	11	4.7 (13.18)	8.0 [-20, 20]	19	8.7 (11.95)	10.0 [-16, 32]
	30min	11	6.4 (11.76)	8.0 [-14, 28]	19	9.5 (10.30)	12.0 [-8, 28]
	60min	11	8.4 (10.42)	8.0 [-12, 28]	19	4.5 (8.19)	2.0 [-10, 22]
	120min	11	6.5 (12.96)	6.0 [-14, 30]	19	2.8 (10.82)	2.0 [-14, 28]

am=ante meridiem; LCM=lacosamide; min=minute; ms=millisecond; PBO=placebo; SD=standard deviation; SS=Safety Set

a Time point relative to start of infusion.

COMMENT: The sponsor found no difference in effects on the PR interval. I conducted analysis of maximum mean and median changes from baseline in PR interval. This analysis suggests a slightly greater PR prolongation in the IV LCM group as compared to the oral LCM group. The maximum PR prolongation with the IV 30 min infusion rate appears to be similar or shorter than with the IV 60 minute rate. The clinical relevance of these small differences is unclear.

Table 74. Maximum mean and median change from baseline in PR interval with oral and IV LCM, SP616.

Maximum Change from Baseline 1 in PR interval	**Oral LCM over 60 min (n=10)**	**IV LCM over 60 min (n=19)**
Mean (SD) ms	3.4 (12.37)[1]	10.2 (13.05)[2]
Median [range] ms	5.0 [-12,18][2]	14.0 [-18, 32][2]
	Oral LCM over 30 min (n=11)	**IV LCM over 30 min (n=19)**
Mean (SD) ms	8.6 (10.42)[3]	9.5 (10.30)[1]
Median PR [range] ms	8.0 [-14, 28] [4]	12 [-8, 28][1]

[1] Observed at 30 minutes after infusion started. [2]Observed 45 minutes after infusion started. [3] Observed 60 minutes after infusion started. [4] Observed 10 minutes after infusion started. Baseline 1= before first LCM IV.

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No clear differences in mean heart rate, QRS interval and QTcF measurements were noted among the treatment groups.

SP 757: There were no differences in mean changes in heart rate across the different infusion duration groups. There was no increase in mean QRS or QTcF in any infusion duration group. There was a small PR prolongation at the end of the infusion for all infusion duration groups.

Again, these two studies were not powered or designed to address differences in the safety profile of the IV and oral formulation or different IV infusion durations.

- Measures of central tendency in healthy volunteers

SP640 – Through QT study

Analysis of central tendency 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. There was no evidence that LCM affects the QRS or prolongs the QT interval, at doses up to 800 mg/day. A table summarizing mean QTc (B) changes in SP640 is presented in the following table. For additional analysis the reader is referred to the review by the QTc team.

Table 75. Changes in QTcI interval in TQTc SP 640

Overall summary of time-matched changes from Baseline in QTcI interval (ms) on Day 6 in twice daily LCM; Thorough QTc trial conducted in healthy male and female volunteers - SP640 (Population: PDS)

Time after last dose	Placebo			LCM 400mg/day			LCM 800mg/day		
	n	mean	SD	n	mean	SD	n	mean	SD
1 hr	54	-3.2	12.7	56	-10.3	15.7	52	-10.7	17.1
2 hr	54	2.6	16.2	56	-6.3	15.2	52	-4.9	12.9
3 hr	53	-3.4	17.4	56	-2.2	15.1	52	-8.0	14.9
4 hr	53	-4.3	15.5	56	-1.7	13.0	52	-6.2	16.0
6 hr	54	-9.1	18.6	56	-11.8	16.9	52	-11.4	16.4
8 hr	54	-9.3	15.0	56	-10.5	16.3	52	-11.1	17.9
10 hr	54	-1.6	18.1	56	-4.6	17.3	52	-7.6	15.9
12 hr	54	-9.1	17.6	55	-9.3	14.8	52	-11.4	15.7

LCM=lacosamide; ms=millisecond; SD=standard deviation; PDS=Pharmacodynamic Set; QT_cI=QT corrected with Individual method

Study SP640 was evaluated by the OND interdisciplinary QT Team. A summary of their conclusions was presented in the Clinical Pharmacology section of this review. The QT review Team did not find any significant effects on the QTc.

Study SP587, a single dose study in healthy male volunteer showed similar results. If something, there seemed to be a shortening in QTc (data not shown).

2) Analyses of marked outliers and dropouts for ECG abnormalities

- ECG Marked outliers EP Pool S1

PR interval outliers were identified as subjects with treatment-emergent ECG values meeting the criteria at any post-Baseline visit during the Treatment Phase. Individual treatment-emergent changes in PR interval were classified as observed values >200ms, >220ms, or >250ms.

Table 76. Subjects with treatment-emergent PR prolongation in EP Pool S1, treatment phase

Parameter criteria	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203
	n/N (%)			
PR interval				
>200ms	15/336 (4.5)	29/260 (11.2)	40/446 (9.0)	14/198 (7.1)
>220ms	10/351 (2.8)	2/264 (0.8)	10/459 (2.2)	1/201 (0.5)
>250ms	0/353	0/264	3/464 (0.6)	1/202 (0.5)

Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Phase (including unscheduled visits) and not meeting the same criteria during Baseline (average of 3 Baseline ECGs prior to dosing). N=number of subjects who have both a Baseline and post-Baseline assessment and did not meet the criteria at Baseline. Source: Sponsor's table in Pg. 291 of ISS.

There was a higher frequency of treatment-emergent PR interval >200ms in the LCM treatment groups (overall, 8.8%) as compared to placebo (4.5%). There was no dose-response. Placebo-treated subjects were more likely to have a treatment-emergent PR interval >220ms (2.8%) than the LCM-treated subjects (overall 1.4%). Four subjects had a treatment-emergent PR interval >250ms, all on LCM (3 subjects in the LCM 400 group and 1 in the LCM 600 group). One of these, subject SP755/106406, on LCM 400 had a single episode of PR interval >250ms, reported as an SAE and leading to discontinuation. For the other 3 subjects the PR interval >250ms was not reported as an AE during the trial, and all 3 subjects completed the trial and transitioned into an open-label extension trial.

Individual treatment-emergent changes in QRS duration were classified as observed values >100ms, >120ms, or >140m. The frequency of QRS duration >100ms treatment-emergent outliers was similar between placebo and the LCM treatment groups and across age groups for EP Pool S1. The frequency of QRS duration >120ms treatment-emergent outliers was somewhat higher in the LCM 400 and 600mg/day groups (2.6% to 3.5%) than in the placebo group (1.4%). There were 2 subjects in the placebo treatment group and 1 subject in the LCM 400mg/day treatment group with QRS duration >140ms.

The sponsor evaluated the QT interval by measuring the QT, QTc (B) and QTc (F) throughout the study and analyzed maximum QTc duration and maximum QTc change from baseline at any post baseline time point in subjects with normal baseline QTc.

The sponsor's analysis of QTc (B) and (F) in EP S1 is presented in the following table:

Table 77. Percentage of patients with prolonged post-Baseline QTc interval (EP S1)

Number and percentage of subjects with prolonged post-Baseline QTc interval during the Treatment Phase in subjects with partial-onset seizures (EP Pool S1)

Parameter criteria	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203	Total N=1308
	n (%)	n (%)	n (%)	n (%)	n (%)
QTcB interval					
≥500ms	0	0	0	0	0
Max increase from BL <30ms	318 (87.4)	230 (85.2)	402 (85.4)	180 (88.7)	1130 (86.4)
Max increase from BL ≥30ms to <60ms	34 (9.3)	34 (12.6)	61 (13.0)	22 (10.8)	151 (11.5)
Max increase from BL ≥60ms	2 (0.5)	1 (0.4)	1 (0.2)	0	4 (0.3)
Max ≥500ms and max increase from BL ≥60ms	0	0	0	0	0
QTcF interval					
≥500ms	0	0	0	0	0
Max increase from BL <30ms	340 (93.4)	248 (91.9)	429 (91.1)	191 (94.1)	1208 (92.4)
Max increase from BL ≥30ms to <60ms	14 (3.8)	16 (5.9)	34 (7.2)	11 (5.4)	75 (5.7)
Max increase from BL ≥60ms	0	1 (0.4)	1 (0.2)	0	2 (0.2)
Max ≥500ms and max increase from BL ≥60ms	0	0	0	0	0

BL=Baseline; LCM=lacosamide; max=maximum; ms=millisecond; QTcB=QT interval corrected using Bazett formula; QTcF=QT interval corrected using Fridericia formula
Note: Baseline=Average of all pre-dose measurements at Visit 3 during the double-blind trial.
Note: Post-Baseline was calculated from all reported values (including unscheduled visits) during the Treatment Phase.

Source: Sponsor's Cardiology report.

APPEARS THIS WAY ON ORIGINAL

As noted in this analysis, no patient presented a prolonged QTc ≥ 500 ms. Maximum QTc changes from baseline (at least once during post-baseline) were categorized in three groups: increase of <30 ms (most of the patients); ≥ 30 to 60ms (119 patients on LCM [12.5%] and 34 patients on placebo [9.9%] or >60 ms (2 patients on placebo [0.5%] and 2 on LCM [0.2%]. Therefore, there is a slightly higher rate of patients with QTc prolongation ≥ 30 to 60ms in the LCM group, but a higher rate of prolongation >60ms in the placebo group.

Of note, the protocol eligibility criteria excluded subjects with a QTc ≥ 450 ms for males or ≥470 ms for females. Once in the study, subjects with QTcB increases ≥60ms above Baseline values or an absolute QTcB ≥500 ms should be discontinued from the protocol.

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- FDA analysis of QTc prolongation in EP 1:

I did an analysis for QTc post-baseline ≥450 ms in males and ≥470 ms in females in EP S1. These values were the cut-off for exclusion to the protocol. A total of 28 subjects had at least one QTc measurement above these values. The listing of these patients and their QTc changes from baseline are presented in **Appendix 20.**

Table 78. Cases of prolonged QTc (post-baseline ≥450 ms in males and ≥470 ms in females) in EP S1

	Placebo	LCM (mg/day)			
		200	400	600	All
	N= 364	N= 270	N= 471	N=203	N= 944
All	n (%)	n (%)	n (%)	n (%)	n (%)
	4 (1.1)	5 (1.9)	16 (3.4)	3 (1.5)	24 (2.5)
Male					
	N= 187	N= 136	N=226	N=92	N=454
	3 (1.6)	2 (1.5)	13 (5.8)	2 (3.3)	17 (3.8)
Female					
	N= 177	N=134	N=245	N=111	N= 490
	1 (0.6)	3 (2.2)	3 (1.2)	1 (1.0)	6 (1.2)

Source: ECG EP S1 datasets submitted in January 2008 (Appendix 19 of this review).

The FDA analysis suggests that the rate of QTc prolongation is higher in the LCM treatment group, as compared to placebo, particularly for the LCM 400 group, and for males more than females. Up to 5.6% of subjects presented at least one post-baseline QTc ≥ 450 ms among men treated with LCM 400. The clinical significant of this finding is unclear. However, an important point to make is that patients with this degree of QTc prolongation were excluded from the LCM studies, therefore it is unknown what the effect of LCM would be in subjects with already prolonged QTc.

- FDA Analysis of Short QTc in EP S1

Short QT has been associated with increased risk of arrhythmia and sudden death. [12] I did a search of cases with QTc <340 ms post-baseline in the EP S1 ECG database. The search found 9 cases, 2 on placebo (0.6%) and 7 (0.7%) on LCM. In all cases the short QTc <340 occurred at a single time. These cases are listed in the following table.

Table 79. Listing of patients with QTc post baseline <340 in EP S1

USUBJID	TRTGRP	VISIT	Short QTc	Baseline QTc	QTc change
667012209	Placebo	VISIT 11	325	380	-55
667015018	Placebo	VISIT 9	338	386	-48
667016926	LCM200	VISIT 12	338	378	-40

[12] Gaita et al. Short QT syndrome: a familial cause of sudden death. Circulation 2003;108.

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USUBJID	TRTGRP	VISIT	Short QTc	Baseline QTc	QTc change
755112317	LCM400	TRANSITION	337	370	-33
755118611	LCM400	TRANSITION	331	358	-26
755122303	LCM400	VISIT 5	314	370	-56
755124205	LCM400	VISIT 6	305	376	-71
755124209	LCM400	VISIT 7	336	355	-19
667015801	LCM600	VISIT 4	328	398	-70

Source ECG datasets, EP S1.

Of note, two of these patients presented other ECG Investigations disorders, one developed First degree AV block, and another developed sinus bradycardia with absent P waves, junctional escape and extrasystoles at the same time that the short QTc was identified.

- Outliers in EP S2 and in studies with IV LCM

Over a longer period of time, treatment with LCM did not appear to increase the incidence of PR interval >250ms. 7 additional subjects had a PR interval >250ms across the various modal dose groups during the open label phase of the studies. None of them was serious or led to withdrawal. The majority of subjects had a PR interval >250ms on only 1 occasion. The time of onset for the PR prolongation was highly variable (Day 29 to Day 1010 on trial).

Table 80. Summary of subjects with treatment-emergent PR prolongation during treatment in subjects with partial-onset seizures (EP Pool S2)

Parameter criteria	LCM modal dose							
	LCM 100mg/day N=79	LCM 200mg/day N=291	LCM 300mg/day N=155	LCM 400mg/day N=383	LCM 500mg/day N=149	LCM 600mg/day N=194	LCM >600mg/day N=76	LCM Total N=1327
	n/N (%)							
PR interval								
>200ms	6/68 (8.8)	28/279 (10.0)	21/149 (14.1)	57/367 (15.5)	16/142 (11.3)	23/183 (12.6)	10/74 (13.5)	161/1262 (12.8)
>220ms	1/70 (1.4)	8/287 (2.8)	6/154 (3.9)	20/379 (5.3)	7/147 (4.8)	9/189 (4.8)	5/76 (6.6)	56/1302 (4.3)
>250ms	1/71 (1.4)	1/287 (0.3)	0/154	5/382 (1.3)	1/147 (0.7)	3/192 (1.6)	0/76	11/1309 (0.8)

Source: Sponsor's table in Pg 293 of ISS.

Prolonged administration of LCM (EP Pool S2) resulted in a higher overall frequency of QRS >100ms values but a similar frequency of QRS >120ms when compared to the placebo and LCM groups from EP Pool S1. There were 4 subjects total who had a QRS duration >140ms in EP Pool S2. Evaluation of outlier data did not identify a QTc prolonging effect for LCM in EP S2.

- Outliers in studies with the IV formulation

b(4)

Analyses of ECG outliers in the phase 1 single-dose and in the multiple-dose (2-5 day) IV epilepsy studies did not find any significant/interpretable signal. Evaluation of outliers in SP616 shows that 15 to 27% of patients had a PR>200 ms, and 30- 40 % had a QRS >100 ms. In SP757, 24%, 15% and 4% had PR >200 ms in the 30 minute, 15 minute and 10 minute infusion, respectively and 22%, 33% and 29% had a QRS > 100 ms in the 30 minute, 15 minute and 10 minute infusion, respectively. These studies were not designed to adequately address small differences in safety between the oral and IV formulation or among different infusion rates. More detailed results of outlier analyses with the IV formulation are presented in **Appendix 21.**

- Outliers among healthy volunteers – SP640

The outlier analysis showed that PR interval outliers most commonly occurred in the LCM 800 mg/day group as compared to the LCM 400mg/day and placebo groups. One patient (1.8%) on LCM 400 had a PR prolongation >220 ms, as compared to 3 on LCM 800 (5.8%) and none on placebo. One subject (LCM 800mg/day) had a treatment-emergent PR interval >250ms.

Table 81. PR interval outliers among healthy volunteers in study SP640 (TQTc)

Summary of subjects with a treatment-emergent PR outlier (SP640 PDS)

Treatment group/time point	Observed criteria[a]		
	>200ms	>220ms	>250ms
	n (%)		
Placebo N=54			
Day 1	2 (3.7)	0	0
Day 3	1 (1.9)	0	0
Day 6	0	0	0
Treatment Phase	2 (3.7)	0	0
LCM 400mg/day N=56			
Day 1	0	1 (1.8)	0
Day 3	1 (1.8)	1 (1.8)	0
Day 6	1 (1.8)	1 (1.8)	0
Treatment Phase	2 (3.6)	1 (1.8)	0
LCM 800mg/day N=52			
Day 1	7 (13.5)	1 (1.9)	0
Day 3	8 (15.4)	2 (3.8)	0
Day 6	7 (13.5)	3 (5.8)	1 (1.9)
Treatment Phase	12 (23.1)	3 (5.8)	1 (1.9)

LCM=lacosamide; ms=millisecond; PDS=Pharmacodynamic Set
a Treatment-emergent outliers are post-Baseline outliers that were not present at the time-matched Baseline.
Data source: 5.3.4.1.1: SP640 Table 12.3.4

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 but there was no clear dose response between LCM 400 and LCM 800. No subject in any treatment group had a QRS duration >120ms during the treatment phase.

The QTc outlier analysis was summarized for the SP640 based on the 12-lead Holter ECG data. The outlier analysis does not suggest a safety concern with QTc prolongation in healthy volunteers. There were no subjects who had a QTcI, QTcB, or QTcF of ≥500ms at any post-Baseline time point. There were also no subjects with an increase in QTcF ≥60ms in either the LCM group or in the placebo group at any time post-treatment. There was 1 placebo-treated

b(4)

subject with an increase from Baseline in QTcI ≥60ms; this occurred in 2 ECG recordings on Day 1. The percentage of subjects with an increase from Baseline in QTcB of ≥60ms was higher in the moxifloxacin and placebo group than in the LCM groups.

Table 82. Subjects with change in QT ≥ 60 ms in SP640

Analysis of subjects with ≥60ms increase from Baseline for uncorrected and corrected interval (QTc) (SP640) (Population: PDS)

Group	N	QT n (%)	QT_cI n (%)	QT_cF n (%)	QT_cB n (%)
Moxifloxacin	52	17 (32.7%)	4 (7.7%)	3 (5.8%)	10 (19.2%)
Placebo	54	10 (18.5%)	1 (1.9%)	0	7 (13.0%)
LCM 400mg	56	4 (7.1%)	0	0	3 (5.4%)
LCM 800mg	52	2 (3.8%)	0	0	2 (3.8%)

LCM=lacosamide; ms=millisecond; PDS=Pharmacodynamic Set; QT_cI, F, B=QT corrected with Individual method, Fridericia method, and Bazett method, respectively.
Data source: 5.3.4.1.1: SP640 Table 8.4.1, Table 9.4.1, Table 10.4.1, Table 11.4.1

Source: Sponsor table in sponsor's Cardiac Safety report.

3) Abnormal ECG morphology findings

- Abnormal morphology in EP S1

b(4)

Trials SP754 and SP755 used a common central ECG over-reader [redacted] and were pooled for an analysis of the frequency of treatment-emergent ECG abnormalities of interest. For the following analysis, a treatment-emergent ECG abnormality was defined as one that occurred at least once during the Treatment Phase but which was not previously observed to be present at the Screening Visit ECG or any of the 3 ECGs collected at Baseline. The following table presents the frequency (including unscheduled visits) of selected treatment-emergent ECG abnormalities in EP Pool S1.

b(4)

Table 83. Summary of subjects with selected treatment-emergent ECG abnormalities during the treatment phase, SP744 and SP745.

b(4)

Class/ECG findings [redacted] cutpoint)	Placebo N=267	LCM 200mg/day N=163	LCM 400mg/day N=363	LCM 600mg/day N=97
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Number of subjects with any finding	**159/260 (61.2)**	**96/161 (59.6)**	**237/362 (65.5)**	**63/96 (65.6)**
Rate[b]				
Rate under 60 sinus bradycardia	29/176 (16.5)	15/110 (13.6)	32/241 (13.3)	7/70 (10.0)
Rate under 45 marked sinus bradycardia	2/260 (0.8)	0/160	3/360 (0.8)	0/95
Rate over 100 sinus tachycardia	4/256 (1.6)	3/159 (1.9)	11/359 (3.1)	4/93 (4.3)
Atrial-related conduction[b]				
PR upper limit for rate and age borderline PR interval (PR interval=200-209ms)	12/238 (5.0)	11/151 (7.3)	19/338 (5.6)	4/94 (4.3)
Prolonged PR interval first degree AV block (PR interval >209ms)	6/252 (2.4)	2/159 (1.3)	8/355 (2.3)	1/95 (1.1)
Ventricular-related conduction[b]				
Broad QRS intraventricular block (QRS duration ≥120ms for age ≤35yr; QRS duration ≥110ms for age ≥36yr)	6/250 (2.4)	3/159 (1.9)	12/339 (3.5)	7/89 (7.9)
Broad QRS, terminal QRS rightward and anterior incomplete right bundle branch block (QRS duration ≥110ms)	2/251 (0.8)	0/159	9/349 (2.6)	4/85 (4.7)
Broad QRS, terminal QRS rightward and anterior complete right bundle branch block (QRS duration ≥120ms)	0/257	0/159	2/360 (0.6)	1/95 (1.1)
Complete left bundle branch block (QRS duration ≥120ms)	0	0	0	0

b(4)

b(4)

Class/ECG findings — cutpoint)	Placebo N=267	LCM 200mg/day N=163	LCM 400mg/day N=363	LCM 600mg/day N=97
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Interval				
QRS -45 to -90, initial axis inferior and rightward consistent with left anterior hemiblock	0/259	0/160	2/360 (0.6)	1/96 (1.0)
QRS axis range 110 to 194 abnormal RAD, could be RVH or left posterior hemiblock	1/260 (0.4)	1/161 (0.6)	1/362 (0.3)	0/96
Repolarization-related[b]				
Borderline QT interval (QT interval ≥450ms if <50yr, ≥460 for women >50yr)	2/257 (0.8)	1/161 (0.6)	4/358 (1.1)	0/94
Prolonged QT interval (QT interval ≥460ms if <50yr, ≥470 for women >50yr)	2/260 (0.8)	0/161	0/362	0/96
Ischemia and infarction-related[c]	6/260 (2.3)	2/161 (1.2)	6/362 (1.7)	3/96 (3.1)

AV=atrioventricular; ECG=electrocardiogram; LCM=lacosamide; RAD=right axis deviation; RVH=right ventricular hypertrophy; yr=years a SP667 is not included in this analysis because a different central ECG laboratory was used (see ISS Section 3.3.1.2). b Subjects who had more than 1 treatment-emergent abnormal finding within this class are counted only once per class for the worst finding within the classification. c Subjects are counted once within the ischemia and infarction-related class if they had at least 1 abnormal treatment-emergent ECG finding with the words "ischemia," "infarct," "or "infarction" in the finding term. Note: Incidence=n of events/N at risk, where: n of events=number of subjects who reported the finding at least once after start of treatment but not pre-treatment. N at risk=number of subjects who had a 12-lead ECG before and after start of treatment who did not have the finding before treatment. For the "number of subjects with any finding" row, N at risk=number of subjects who had a 12-lead ECG before and after start of treatment. PG 130 of Cardiac safety report.

Review of this table (that includes 2 of the 3 placebo controlled epilepsy studies that share the central reading institution) shows that the frequency of abnormal ECG findings was generally similar for the placebo and LCM treatment groups with the exception of the finding of ventricular-related conduction abnormalities, particularly **broad QRS (with or without intraventricular block and complete or incomplete right bundle branch block), which was 3% in the placebo group (8/267) and 12% (12/97) in the LCM 600mg/day group.** The clinical significance of this finding is unclear.

First degree AV block was not a common finding by the over-reader and similar frequencies were observed in the placebo (2.4%) and the LCM groups (≤ 2.3%). There were no findings of second degree AV block.

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Bradycardia was reported at a similar frequency in the placebo and LCM treatment groups. However, sinus tachycardia was reported at a higher rate in the LCM 400 and 600 mg groups as compared to LCM 200 and placebo.

- Abnormal ECG morphology findings in thorough QT/QTc trial SP640

In general, the number of subjects who had an abnormal ECG finding was similar at Baseline and post-Baseline for all treatment groups and was similar across the treatment groups, except for First degree AV Block in LCM 800. There is also a suggestion for a higher rate of intra-ventricular conduction defects with LCM 400 and 800. A summary of selected treatment emergent ECG abnormalities in this study is presented in the following table.

Table 84. Selected treatment emergent ECG abnormalities in SP60 (pharmacodynamic set)

ECG findings (eRT central ECG cutpoint)	Placebo N=54	LCM 400mg/day N=56	LCM 800mg/day N=52
	n (%)	n (%)	n (%)
Sinus bradycardia (heart rate <50bpm)	9 (16.7)	1 (1.8)	3 (5.8)
Sinus tachycardia (heart rate >100bpm)	30 (55.6)	27 (48.2)	31 (59.6)
First degree AV block (PR interval >200ms)	3 (5.6)	2 (3.6)	11 (21.2)
Intraventricular conduction defect (QRS duration >110ms)	0	2 (3.6)	2 (3.8)
T Waves (flat, biphasic, or inverted)	20 (37.0)	17 (30.4)	19 (36.5)
Prolonged QTc (QT interval >499ms)	3 (5.6)	3 (5.4)	1 (1.9)

Source: sponsor's Cardiac Safety Report, page 46.

SUMMARY OF ECG FINDINGS

There is evidence that LCM has a dose-related effect in the heart conduction system, particularly the PR and QRS interval.

ECG evaluations in EP S1 suggest that LCM did not affect mean heart rate at therapeutic doses. There was a dose-related increase in mean PR interval change from Baseline among the LCM treatment groups in EP Pool S1. 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,

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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 600 treatment group. The difference with placebo mean maximum QRS increase was -0.9ms, 0.5ms, and 0.4ms in 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 Bazzet (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.

The ECG outlier analysis in EP S1 found a higher percentage of patients with a PR>200 ms in LCM as compared to placebo (the rate was 4.5%, 11.2%, 9% and 7.1% in the placebo, LCM 200, LCM 400 and LCM 600 groups, respectively). There was also a higher percentage of patients with a QRS>120 ms in LCM treated patients as compared to placebo (the rate was 1.4% , 2.6 and 3.5% in the placebo, LCM 400 and LCM 600 groups, respectively). Regarding the QTc, no patient presented a QTc>500 ms, however, more patients had an increase from baseline between 30-60 ms in the LCM treatment group. An analysis of treatment emergent QTc(B)≥450ms in male and ≥ 470 ms in women (which were the exclusion criteria in the protocols) shows more outliers in the LCM 400 and 600 m/day groups (3.4% and 1.5% , respectively) as compared to placebo or LCM 200 (1.1%). Age appeared to increase the risk of PR and QRS prolongation.

The outlier analysis in SP 640 showed that PR interval outliers most commonly occurred in the LCM 800 mg/day group as compared to the LCM 400mg/day and placebo groups. One patient (1.8%) on LCM 400 had a PR prolongation >220 ms, as compared to 3 on LCM 800 (5.8%) and none on placebo. One subject in the LCM 800 mg/day group had a treatment-emergent PR interval >250ms. No subject in any treatment group had a QRS duration >120ms during the treatment phase. No subject had a QTcI, QTcB, or QTcF of≥500ms at any post-baseline 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).

7.1.10 Immunogenicity - Not Applicable

7.1.11 Human Carcinogenicity

There is no evidence of carcinogenicity in non-clinical studies. Evaluation of deaths, serious AE, discontinuations due to AE and common AE under the MedDRA SOC Neoplasms benign, malignant and Unspecified (including cysts and polyps) in the LCM clinical program did not suggest an increased risk of malignancy in patients taking LCM.

7.1.12 Special Safety Studies – Not applicable

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor did an evaluation of tolerability and abuse potential and concluded that there does not appear to be risk for abuse potential. Based on study 903, there is evidence of abuse potential for the 800 mg dose.

- Potential for abuse in SP 903

Study SP903 was a double blind, randomized, single dose crossover oral tablet study specifically designed to address potential for abuse. The study included 76 male and female subjects with a prior history of abuse. It compared LCM 800 mg/day and 200 mg/day to high (3 mg) and low doses (1.5 mg) of lorazepam, and placebo. A total of 17 subjects had a reported PT of euphoric mood, corresponding to the lower level terms euphoria, feeling high, euphoric mood. The PT euphoric mood in this study did not include terms such as feeling drunk and feeling abnormal. There were five cases of euphoric mood with LCM 800 (14.7%), vs. one with LCM 200 (2.9%) and one with placebo (2.9%). Euphoric mood was also reported in 11.8% of subjects on alprazolam 1.5 mg and 9.1% of subjects on alprazolam 3 mg. In general, LCM 800 behaved similarly to low dose alprazolam. This study is reviewed in detail by Katherine Bonson, Ph.D., Controlled Substance Staff.

- Potential for abuse in phase 1 studies other than SP 903

There were 12 patients with reports of euphoric mood in phase 1 studies other than SP903. An analysis of subjects with the PT euphoric mood, excluding subjects for which the LLT was "feeling drunk" or "feeling abnormal" is presented in the following table.

Table 85. Patients with lower level term of euphoric mood in phase 1 studies other than SP903

Study	Study design	Patients with lower level terms of euphoria, feeling happy, elevated or euphoric mood
SP587	OL, single ascending oral dose (n=16M)	3 (ID8016, 8007 & 8014) with LCM 400, 600 & 800 mg/day. Patient 8007 & 8016 also had "illusion".
SP588	DB, R, PC, Multiple dose (16 days), oral capsule ascending dose (n=33M) N=24 LCM/9 Plac. 300 or 500 mg once or bid	2 (ID 8004 & 8053, with LCM 600 500 mg/d, respectively).
SP660	OL, single and multiple dose, interaction with metformin (M)	1 (ID 80005) with LCM 400 mg/d

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Study	Study design	Patients with lower level terms of euphoria, feeling happy, elevated or euphoric mood
SP618	OL, multiple dose, carbamazepine (CBZ) interaction (n=20 M)	(ID#8011, on day 7, after first LCM dose; ID#8008, on day 15, after first LCM 100 mg dose. (Subjects were on prior CBZ).
SP644	DB, PC, R crossover, digoxin interaction (n=23 M)	2 (ID 80016 & 81010), with LCM 400 mg/day.
SP599	OL, oral capsule, Mycrogynon® interaction (n= 40 F)	2 (ID 8005 & 8021), with LCM 400 mg/day.

Of note, no cases of euphoric mood were reported in subjects receiving placebo in SP588 and SP644. The other Phase 1 studies were not placebo-controlled.

- Potential for abuse in phase 2/3 studies with epilepsy.

There were 3 patients with PT elevated/euphoric mood in this population, two during the placebo-controlled phase (one on LCM 600 and another on LCM 400, the later considered serious and requiring discontinuation) and one during the OL phase. The cases are listed in **Appendix 22.** Another PT term that could be associated with an increased potential for abuse is hallucinations.

The following table lists treatment emergent adverse events (TEAEs) under the MedDRA HLT term "perceptions disturbances."

Table 86. TEAEs under the HLT term "perception disturbances" EP S1 and EP S2

ID	Part /TRTGR	LCM Dose	PT	Action	Outcome	Rel st day
Placebo-controlled (EP S1)						
667018817	DB/ LCM 600	400	Hallucination, visual	None	R	23
754011807	DB/ LCM 400	200	Hallucination	None	R	16
768112407	DB/ LCM 400	100?	Hallucination, visual	None	Not R	3
Open label extensions						
743014204	OL	400	Hallucination	None	R	?
830111802	OL	500	Hallucination	Drug interrupted	R	?
607001055	OLE	500	Hallucination, visual	None	R	78
	OLE	600	Deja vu	None	R	483
607001251	OLE	400	Hallucination	None	R	190
	OLE	400	Hallucination (post Sz)	None	R	369
	OLE	500	Hallucination	Dose reduced	R	76
	OLE	600	Hallucination	None	R	891
667011008	OLE	600	Hallucination	None	R	903
667017722	OLE	400	Illusion	WITHDRAWN	Not yet R	171
754010608	OLE	400	Hallucination, auditory	Dose reduced	R	243
754010610	OLE	400	Hallucination, auditory	None	R	199
	OLE	400	Hallucination, visual	None	R	155
	OLE	700	Hallucination, visual	None	R	383
754011213	OLE	600	Hallucination, visual	None	Not R	652
754012101	OLE	800	Hallucination	Dose reduced	R	551
	OLE	100	Hallucination	Dose reduced	R	6
754012902	OLE	300	Hallucination, visual	WITHDRAWN	R	145
755124603	OLE	400	Hallucination, auditory	Dose not changed	NR	293

Source: AE datasets submitted with SUR. DB= double blind. OL= Open label. OLE= Open label extension.

Fifteen subjects reported at least one treatment emergent adverse event under the HLT perception disturbances. Three of them occurred during the double blind phase of the studies (EP S1), all three in the LCM randomized group (the dose taken by one patient is unknown). Twelve AE of hallucination were reported in the OL studies, however, in the absence of a control arm this finding is difficult to interpret.

The rate of euphoria in the phase 2/3 epilepsy studies was 2/944 (0.2%) vs. 0/781 (0%). Of note, the phase 2/3 placebo-controlled studies did not included the 800 mg/day dose. Although several of the OL studies allowed flexible dose up to 800, the exposure to doses > 600 mg/day is small (n=76).

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In summary, study SP903 provides a strong suggestion that LCM has potential for abuse at the 800 mg/day dose. In this study, LCM 800 behaved similarly to 3 mg of alprazolam. Studies SP644 and SP588 (placebo controlled phase 1 studies) and the phase 2/3 epilepsy studies also suggest that LCM might be associated with abuse potential at lower doses, with cases of euphoria on LCM 400-600 and hallucinations at doses of 100 to 400 mg/day, but no cases on placebo.

The Controlled Substances Staff has reviewed this application and concluded that LCM has abuse potential. CSS is preparing an Eight Factor Analysis that recommends placement of Lacosamide into Schedule IV of the Controlled Substances Act (CSA). For additional details the reader is referred to Dr. Benson's review.

7.1.14 Human Reproduction and Pregnancy Data

There were three pregnancies in the epilepsy studies (reported under the Pregnancy, puerperium and perinatal MedDRA SOC). Two were discovered because of spontaneous abortions and did not lead to drug withdrawal (one during the double-blind phase, one during the OL phase) and one that was detected on relative day 288 of the LCM treatment and led to drug withdrawal. The outcome of the pregnancy in this case is unknown. The cases are as follows:

Table 87. Cases of Pregnancy in EP S1

ID	PT	Rel day on LCM	Part	LCM Dose
667016808	Pregnancy (S) (W)	233	OLE	200
755112313	Abortion missed (S)	48	DB	400
755114109	Abortion spontaneous (S)	48	OLE	100

S: Serious. W: led to withdrawal.

There is limited information for LCM in patients who are pregnant. The Pharmacology-toxicology review is pending at the time of this review.

7.1.15 Assessment of Effect on Growth – Not Applicable

7.1.16 Overdose Experience

There is limited overdose experience with LCM. A small number of patients were exposed to doses above the maximum proposed dose for approval (600 mg/day). The open label studies allowed doses up to 800 mg/day. Nine patients received doses above 800 mg/day in pool S2. Of these, only one was identified as intentional. The narrative of this case is as follows:

- Subject ID# 774/755110406 was a 25-year-old white female with a past medical history of epilepsy who was assigned a dose of LCM 600mg/day in SP774. She attempted suicide by taking approximately 12 grams of LCM, 0.7 grams of zonisamide, 20 grams of topiramate and 50 grams of gabapentin. She presented in a coma (Glasgow coma scale 3) following a seizure cluster and was hospitalized. She recovered 2 days later, but developed a pneumonia due to aspiration which was treated and recovered.

The remaining incidences of subjects exposed to LCM > 800mg/day were assessed as accidental. Adverse events associated with doses of LCM >800 mg for those patients who had AEs were dizziness, fall, musculoskeletal stiffness, nausea and vomiting. These events by patient are presented in Table 85.

Table 88. AE with onset al LCM doses greater than 800 mg/day

Subject	Days on >800mg/day dose	AE(s) with onset at LCM doses >800mg/day dose	Serious (Y/N)	Intensity	Relationship	Outcome
LCM 900mg/day						
607001705 (10380 in SP615)[a]	1	Musculoskeletal stiffness	N	Mild	Probable	Recovered/resolved
667010901 (10601 in SP615)	1	None	NA	NA	NA	NA
667012005 (10879 in SP615)	2	None	NA	NA	NA	NA
667013001 (11076 in SP615)	1	None	NA	NA	NA	NA
754016019	1	None	NA	NA	NA	NA
755124205	14	Fall	N	Moderate	Possibly	Recovered/resolved
		Skeletal injury	Y	Severe	Unlikely	Not recovered/not resolved
		Tooth fracture				
LCM 1050mg/day						
754015607	1	Anxiety	N	Mild	Possibly	Not recovered/not resolved
754016017	1	Decreased visual acuity	N	Moderate	Highly probable	Recovered/resolved
		Dizziness				
		Nausea				
		Dysarthria				
		Vomiting				
754016014	1	None	NA	NA	NA	NA

a Subject 607001705 (10380 in SP615) received LCM 900mg/day and 1200mg/day and thus is represented twice on the table. The AE of musculoskeletal stiffness began on 22 Mar 2002 at a dose of LCM 900mg/day and continued until 24 Mar 2002, when the subject was on a dose of LCM 1200mg/day. The AE ended on 24 Mar 2002, 1 day prior to the LCM dose being reduced on 25 Mar 2002. Source: March 17, 2008 response to FDA request.

7.1.17 Postmarketing Experience

Not Applicable

7.2 Adequacy of patient exposure and safety assessments

7.2.1 Description of Primary Clinical Datasources (population exposed and extent of exposure) used to evaluate safety

A summary of studies for the epilepsy indication was presented in Section 4 of this review.

7.2.1.1 Demographics

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The patients in the studies for partial-onset seizures with the tablet formulation had a mean age of 38.6 years (EP Pool S1) and 38.7 years (EP Pool S2). Both males and females were well-represented. The mean time since epilepsy diagnosis was over 23 years. The lifetime use of other AEDs was 4 or more in 80% of patients and 7 or more in 45% of patients. Eighty five percent of patients were taking 2 or 3 concomitant AED during the study. Concomitant AED use was typical of the epilepsy population and was generally similar across LCM dose groups. Common concomitant AEDs were carbamazepine, lamotrigine, levetiracetam, valproate, and topiramate.

Demographic and baseline characteristics were generally similar across regions (ie, US and Europe/Australia), except for race and BMI. In addition, subjects in US-based trials had taken a greater number of lifetime AEDs upon enrollment and reported more concomitant diseases. In EP Pool S1, only 110 (8.4%) subjects were Non-White (4.3% were Black, 0.8% were Asian, and 3.4% were "Other").

Demographics in EP Pool S1 are presented in the following table:

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Table 89. Demographics of the EP Pool S1 population

Parameter	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203	Total N=1308
Age (years)					
Mean (SD)	38.5 (11.25)	38.1 (11.78)	39.2 (12.44)	38.1 (11.18)	38.6 (11.79)
Min, Max	16, 66	16, 66	16, 71	16, 69	16, 71
<65 years, n (%)	362 (99.5)	267 (98.9)	459 (97.5)	202 (99.5)	1290 (98.6)
≥65 years, n (%)	2 (0.5)	3 (1.1)	12 (2.5)	1 (0.5)	18 (1.4)
Gender, n (%)					
Male	187 (51.4)	136 (50.4)	226 (48.0)	92 (45.3)	641 (49.0)
Female	177 (48.6)	134 (49.6)	245 (52.0)	111 (54.7)	667 (51.0)
Race, n (%)					
White	334 (91.8)	260 (96.3)	423 (89.8)	181 (89.2)	1198 (91.6)
Black	18 (4.9)	5 (1.9)	23 (4.9)	10 (4.9)	56 (4.3)
Asian	2 (0.5)	2 (0.7)	5 (1.1)	1 (0.5)	10 (0.8)
Other	10 (2.7)	3 (1.1)	20 (4.2)	11 (5.4)	44 (3.4)
BMI (kg/m^2)					
Mean (SD)	26.4 (5.64)	25.6 (5.04)	27.5 (6.76)	27.3 (6.43)	26.7 (6.12)
<18.5, n (%)	17 (4.7)	9 (3.3)	16 (3.4)	7 (3.4)	49 (3.7)
18.5 - <25, n (%)	141 (38.7)	126 (46.7)	174 (36.9)	72 (35.5)	513 (39.2)
25 - <30, n (%)	125 (34.3)	81 (30.0)	143 (30.4)	69 (34.0)	418 (32.0)
≥30, n (%)	81 (22.3)	53 (19.6)	135 (28.7)	54 (26.6)	323 (24.7)
Missing	0	1 (0.4)	3 (0.6)	1 (0.5)	5 (0.4)
Geographic region, n (%)					
US	158 (43.4)	60 (22.2)	264 (56.1)	155 (76.4)	637 (48.7)
Europe/Australia	206 (56.6)	210 (77.8)	207 (43.9)	48 (23.6)	671 (51.3)

BMI=body mass index; LCM=lacosamide; Max=maximum; Min=minimum; SD=standard deviation; US=United States. Source: Sponsor's table in page 44 of the ISS.

As per the table above, a small number of patients older than 65 years were included in the phase 2/3 epilepsy studies (18/944= 1.4%). Of note, the highest percentage of elderly patients was in LCM 400 mg/day randomization group (2.5% as compared 1.1 in the LCM 200 and 0.5% in LCM 600 and placebo), which may explain in part why this group is usually the one with the highest percentage of adverse events throughout all the analyses in this review.

The demographics of this population of subjects with partial-onset seizures appear to be representative of the population to which the drug will be marketed, with the exception of race and age.

The issue of race has been adequately addressed in a clinical pharmacology study in subjects of different ethnicity.

The percentage of subjects with partial-onset seizures greater than or equal to 65 years of age was small. Only 18 patients were ≥ than 65 years in the entire EP SP2 database. This limitation has been addressed in part by a PK Phase 1 trial (SP620) of LCM in elderly and young subjects and by the exposure in patients treated in the DNP studies (in DNP Pool S2, 447 subjects were ≥65 years of age and of those, 72 subjects were ≥75 years of age). These subjects received LCM as a monotherapy at doses similar to those used in the epilepsy trials.

The sponsor proposes to use — IV formulations in patients age 16 years and older. However, only 7 patients who were 16 or 17 years old received LCM in these studies (n=3 and n=4, respectively). Moreover, no patient younger than 18 was exposed to the IV formulation. I would recommend that the minimum age for using LCM should be 18 years old. b(4)

- Baseline concomitant diseases and concomitant medications in EP S1

The table of concomitant diseases at the time of entry to EP S1 (sponsor's Table EP 4.1.1.of the original application) only included those diseases presented by at least 5% of subjects. The table of concomitant meds at the time of entry to EP S1 (Table EP 5.1.1 of the original application) only included those meds taken by at least 10% of subjects. The FDA requested tables with a full list of medications and diseases presented by these patients at baseline. This information was submitted on 5/16/08 (although to be precise, the information refers to patients at screening).

Regarding concomitant diseases at baseline, Cardiac disorders were present in 2.4% of patients in the LCM group and 4.7% of patients in the placebo group. Beta blockers were taken by 3.5% of patients in the LCM treatment group and 5.2% of patients on placebo; calcium channel blockers were taken by 1.4% of patients in the LCM and 1.6% of patients on placebo; "cardiac therapy" was taken by 0.7% of patients in the LCM treatment group and 1.1% of those on placebo. Therefore, overall there was a small percentage of patients with cardiac disorders and taking cardiac and antihypertensive medications in the entire epilepsy program, and there was a trend for more of these patients being in the placebo group. A summary of the concomitant diseases and medications at screening are presented in **Appendix 23** of this review.

Of particular interest is whether patients in the IV pool represent the population in which it will be used. Only 3 patients were taking beta blockers in the 15-minute infusion rate group, and one

of them presented profound bradycardia. Of note, **only one patient >65 years of age was included in the IV safety pool.** Moreover, patients in the phase 2/3 studies with the IV formulation were recruited from patients receiving LCM for weeks to months during the open label extension studies.

- Patient excluded from the phase 2/3 epilepsy studies

The sponsor has been asked to provide a summary table of all patients who were screened for phase 2/3 epilepsy studies but did not fulfill eligibility criteria. This information is pending at the time of this review.

7.2.1.2 Extent of exposure (dose/duration)

As per the original submission a total of 1327 unique subjects with partial-onset seizures received LCM in Phase 2 or 3 trials during the development program.

In EP Pool S1, approximately 65% of subjects had a mean daily dose of LCM 200mg/day to 600mg/day, and approximately 98% of subjects had a maximum daily dose of LCM 200mg/day to 600mg/day. The overall average exposure to LCM in EP Pool S1 was 95.8±37.33 days. The total subject-years (PYRs) of exposure to LCM in EP Pool S2 was 1803.0 PYRs. The greatest subject-years of exposure occurred with LCM 400mg/day (504.2 PYRs).

In EP Pool S2, approximately 88% of subjects (1172/1327 subjects) had a modal dose of LCM 200mg/day to 600mg/day. The term modal dose refers to the dose most commonly used during the study by an individual subject. Across all durations, most subjects (60.4%; 802/1327 subjects) had a modal dose of LCM ≥400mg/day and 31.6% (419/1327 subjects) had a modal dose of LCM ≥500mg/day. Of the 802 subjects who had a LCM modal dose ≥400mg/day, 686 had LCM for ≥6 months and 553 had LCM for ≥12 months.

> *Comment: This exposure fulfills minimum ICH guidelines for patient exposure (300 patients for at least 6 months and 100 patients for 1 year at the recommended dose range) for the tablet formulation.*

Across all durations in EP Pool S2, 81.7% of subjects received a maximum daily dose of LCM ≥400mg/day and 52.4% of subjects received a maximum daily dose of LCM ≥500mg/day. At the time of the original application (cut-off 10/16/06) the mean treatment duration for the 1327 subjects in EP Pool S2 was 496.3 days. The median modal dose was LCM 400mg/day and the median maximum daily dose was LCM 500mg/day.

A summary of the overall exposure to LCM by length of exposure in EP S2 at the time of the original application and at the time of the 120-day SUR is presented below. As seen in this table, the SUR added approximately 400 PYRs of exposure to the one in the original application.

b(4)

Table 90. Overall exposure to Lacosamide oral tablet in partial onset seizure population (EP S2) as of June 12, 2007

	Total number of subjects	PYRs of exposure	Total number of subjects	PYRs of exposure
	Original application		SUR (cut off 6/12/07)	
>0 months	1327	1803.0	1327	2214.0
>6 months	983	1746.6	1000	2162.9
>12 months	778	1603.1	852	2062.3
>24 months	329	975.6	590	1704.4
>36 months	179	651.6	213	854.2
>4 months	115	459.2	177	746.5
>48 months	69	300.9	129	578.9
Last visit	1327	1696.0	1327	2088.8

a Percentages based on number of subjects within each respective pool exposed at least once to LCM.
b Subject-years of exposure at time points greater than 0 months (eg, 6 months, 12 months) represents subject-years of exposure for the subjects who made it past the respective time point. Source: pg. 22 Summary of Clinical Safety, and 33 of SUR.

Table 91. Exposure to oral tablet LCM by mean modal dose/duration,Treatment phase (10/16/08)

Table 90.a. Exposure in EP S1

Duration (days)	LCM (mg/day) N=924						
	0-<100	100-<200	200-<300	300-<400	400-<500	500-≤600	Any dose
	n (%)						
1-14	1 (0.1)	39 (4.2)	0	0	0	0	40 (4.3)
15-28	1 (0.1)	33 (3.6)	29 (3.1)	0	0	0	63 (6.8)
29-42	0	14 (1.5)	30 (3.2)	13 (1.4)	0	0	57 (6.2)
43-56	0	2 (0.2)	1 (0.1)	13 (1.4)	1 (0.1)	0	17 (1.8)
57-70	0	4 (0.4)	1 (0.1)	7 (0.8)	3 (0.3)	0	15 (1.6)
71-84	0	1 (0.1)	1 (0.1)	5 (0.5)	3 (0.3)	0	10 (1.1)
85-98	0	111 (12.0)	1 (0.1)	2 (0.2)	3 (0.3)	0	117 (12.7)
99-112	0	111 (12.0)	19 (2.1)	88 (9.5)	1 (0.1)	0	219 (23.7)
113-126	0	1 (0.1)	21 (2.3)	136 (14.7)	10 (1.1)	25 (2.7)	193 (20.9)
≥127[b]	0	0	10 (1.1)	93 (10.1)	38 (4.1)	52 (5.6)	193 (20.9)
Any duration	2 (0.2)	316 (34.2)	113 (12.2)	357 (38.6)	59 (6.4)	77 (8.3)	924 (100)

b(4)

Table 90.b. Exposure in EP S2

Duration (days)	LCM modal dose (mg/day) N=1327 n (%)							
	0-<100	100-<200	200-<300	300-<400	400-<500	500-≤600	>600	Any dose
91-181	0	5 (0.4)	32 (2.4)	10 (0.8)	37 (2.8)	14 (1.1)	0	98 (7.4)
182-364	1 (<.1)	3 (0.2)	48 (3.6)	37 (2.8)	83 (6.3)	46 (3.5)	4 (0.3)	222 (16.7)
365-729	0	7 (0.5)	70 (5.3)	64 (4.8)	144 (10.9)	155 (11.7)	35 (2.6)	475 (35.8)
730-1094	0	0	9 (0.7)	12 (0.9)	36 (2.7)	53 (4.0)	14 (1.1)	124 (9.3)
≥1095	0	2 (0.2)	14 (1.1)	19 (1.4)	32 (2.4)	61 (4.6)	23 (1.7)	151 (11.4)
Any duration	2 (0.2)	77 (5.8)	291 (21.9)	155 (11.7)	383 (28.9)	343 (25.8)	76 (5.7)	1327 (100)

a Treatment Phase= Titration Phase plus Maintenance Phase (up to 126 days). b Subjects could receive treatment within a window for the interim and final Maintenance Visit. Based on the allowable visit windows and the reserve LCM provided on the weekly blister cards, the max. duration of exposure for a subject could be up to 163 days. Mean daily dose= the cumulative (daily) dose divided by the total exposure duration (in days). Exposure to placebo during the Titration Phase for subjects randomized to LCM 200mg/day or 400mg/day is not included in the calculation of mean daily dose. Source: Clinical summary, pg 25 and 27

7.2.1.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

7.2.1.4 Adequacy of Overall Clinical Experience

The clinical experience appears acceptable to support the partial onset seizure indication. There were relatively few elderly patients exposed to LCM in the partial onset seizure population (only 16), however, there is some additional experience in the elderly from DNP studies.

The studies had stringent eligibility criteria that excluded patients with heart conditions and taking certain concomitant medications that could increase or confound the potential CV toxicity of LCM. Additionally, antipsychotics, anxiolytics, MAO inhibitors and antihistaminics, were also exclusionary medications. b(5)

. In the meantime, the label should carry a WARNING regarding the unknown risks in these population.

No naïve patients were exposed to intravenous LCM in the phase 2/3 studies. All patients in these studies had been exposed to oral LCM for several months before being exposed to the IV formulation. Therefore, subjects in the IV pool are extremely healthy and have proven to have tolerated oral LCM well. Only one subject was older than 65 in the entire IV pool. There is insufficient data to support the use of the IV formulation in subjects older than 65 years, in naïve patients and in patients with prevalent concomitant diseases (e.g ischemic heart disease).

b(4)

Non-White ethnic groups are under-represented in the database. This potential limitation has been addressed by a Phase 1 trial of LCM to study the PK and safety in White, Black, and Asian subjects. The number of subjects is small to address differences in adverse event rates.

Children and adolescents (<16 years old) have not been studied with LCM. At this time, LCM will not be recommended for use in patients — years of age. The potential off label use of LCM [redacted] is of concern. b(4) b(4) b(5)

In addition, pregnant or lactating women have not been studied with LCM. Therefore, as a precautionary measure LCM should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Because many drugs are excreted in human milk, a decision on whether to discontinue breast-feeding or discontinue therapy with LCM should be made taking into account potential benefits and risks.

7.2.2 Adequacy of Special Animal and/or In Vitro Testing

This is being addressed by the Pharmacology-toxicology reviewer.

7.2.3 Adequacy of Routine Clinical Testing

In general, the clinical testing appears adequate. Of note, no measurements of prothrombin time were done in these studies.

7.2.4 Adequacy of Metabolic, Clearance, and Interaction Workup

This is being addressed by the Clinical Pharmacology and Biometrics reviewers.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.

As mentioned throughout the review, there is a clear effect of LCM in the heart conduction system. 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. The studies had a long list of exclusionary medications. Some patients with cardiovascular conditions were included in the DNP database and may help to address this issue without the need of an additional study before approval. However, the population in the IV LCM studies is subset of an already healthy population who tolerated LCM well for months before being exposed to the IV formulation. I would recommend IV LCM should not be allowed in naïve patients.

7.2.6 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data are acceptable. Several request for clarification were sent by the FDA to the sponsor throughout the review cycle and adequately addressed by the sponsor.

b(4)

In general, patients with AE of interest were followed until resolution, however, a small number of subjects was lost to follow up, including one case with transaminases >5x ULN, confounded by alcohol use. Another subject who developed drug-induced hepatitis/nephritis did not have measurements of bilirubin and prothrombin time at the time of the transaminase elevation therefore, an adequate assessment of hepatic function at the time of the event, can not be done. Moreover, prothrombin time was not measured in the clinical program. Any further studies should include measurements of prothrombin time, particularly in subjects with elevated transaminases.

During review of the Cardiac Report, this reviewer became aware of the fact that site 012 was discontinued from participation in study 667 because of non-compliance. As per the letter sent by the sponsor to the investigator, the reason for termination of the study participation its the inability of the site to comply with the signed agreement because the investigator would not be available to conduct all required neurological examinations and review ECGs as required by the protocol. The non-compliance was identified by the sponsor during a site visit. The site involved subjects 66711201, 11205, 11206 and 11207. Efficacy and safety results from this site are unlikely to impact the overall assessments.

Most CRFs contain an automatic ECG report that was limited to "Normal", "Abnormal, clinically significant, "Abnormal, not clinically significant" without description of the abnormality. For further submissions or other applications it would be desirable that a copy of every ECG that is abnormal be included in the CRF, or at least that the "abnormality" be specified in the report. However, the narratives contain additional information on ECG findings.

7.2.7 Additional Submissions, Including Safety Update Report

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 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 overall exposure to LCM in all studies for all indications was 3639 unique subjects, or 3377.6 PYRS of exposure. 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.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Interpretation of the safety data is somewhat limited because of the forced titration study design and even more complicated for the long term safety pool, because of the addition and or change in dose of LCM and concomitant medications.

There were nine deaths in the epilepsy program (one during the placebo-controlled phase). Four of them are consistent with SUDEP (none of them in the placebo-controlled phase). The rate of SUDEP in this program is within the rate reported in patients with severe epilepsy. There were 15 deaths in the neuropathic pain program. Eight were cardiac related. Three deaths occurred during the placebo-controlled phase (all cardiac related in patients taking LCM).

Most of the AEs occurred during the titration phase. The most common drug related events were dizziness, ataxia, nystagmus, tremor. The most common serious AE and discontinuations due to AE were also in the Nervous system disorders SOC. In terms of AEs, there is a clear dose response for doses of $\geq$ 400 mg/day, as compared to 200 mg/day, however, because of the study design and the smaller number of patients randomized to the LCM 600 group, it is unclear whether the 600 mg/day dose is associated with a higher AE rate than the 400 mg/day dose.

Less common but relevant adverse events were cardiac toxicity and liver toxicity. The most common cardiac effects were a prolongation in the PR and QRS intervals. There were no cases of second degree AV block or serious arrhythmias in the epilepsy or phase 1 studies database, but there were two cases of bradycardia with junctional escape, one in a phase 1 study with the oral table and one in a phase 2/3 study with the IV formulation. Syncope seems to be associated with LCM however the mechanism is unclear. Most patients with syncope did not have an ECG at the time of the event. A few cases who had an ECG done at the time of the syncope showed no ECG changes, except for one case of syncope associated with PR prolongation in a healthy subject in the digoxin interaction study. There was evidence of a potential for liver toxicity. There was one case of hepatitis and nephritis with and extensive workup - that was negative-, shortly after completion of one of the phase 1 studies. Of note, this patient did not have bilirubin measurements at the time of the event. This case was interpreted as a drug hypersensitivity reaction. The label should carry a WARNING for potential hypersensitivity reactions.

Another AE of concern with LCM is depression and suicidality. The rate of suicidality in the epilepsy program was 5/944= 0.5 among LCM-treated patients and 1/781= 0.1% among those who received placebo. The rate is similar to that recently described for other AEDs. The label should carry a WARNING (Class labeling) for the risk of suicidality.

PR interval prolongation was identified in all population studied. In most cases was asymptomatic, however, more serious AV block is anticipated to occur in patients with underlying CV disease, conduction abnormalities and patients taking medications that prolong the PR interval. In the controlled neuropathic pain population, 13 cases of syncope were

observed in patients treated with LCM as compared to none on placebo (1.2% vs. 0) and seven cases of atrial fibrillation/ flutter were observed in LCM treated patients as compared to none on placebo.

The size of the LCM oral tablet database and analyses conducted in this database appear adequate to support the safety in chronic use in patients with partial onset epilepsy at doses of 200 to 600 mg daily. Based on the clear dose-response in terms of safety and the lack of an efficacy advantage of LCM 600 over LCM 400, I think that the maximum recommended dose should be [redacted] mg daily. b(4)

7.4 General Methodology

7.4.1 Pooling data across studies to estimate and compare incidence

Safety results from combined studies (Pool EP S1, EP S2, IV and oral capsule) were shown throughout this review. As mentioned earlier, the safety in neuropathic pain studies is being reviewed by DAARP. The disposition in EP S1 is presented in the following table.

Table 92. Subject disposition in EP Pool S1, FDA analysis

	PLACEBO	LCM 200	LCM 400	LCM 600
	N (%)	N (%)	N (%)	N (%)
COMPLETED	317(86.8)	221(81.9)	364(77.1)	126(61.8)
DID NOT COMPLETE	**48(13.2)**	**49(18.1)**	**108(22.9)**	**78(38.2)**
Reason for withdrawal	N(%)*	N(%)*	N(%)*	N(%)*
Adverse event	**18(37.5)**	**26(53.1)**	**81(75.0)**	**58(74.4)**
Lack of efficacy	5(10.4)	3(6.1)	2(1.9)	2(2.6)
Lost to follow up	3(6.3)	1(2.0)	.	.
Other reasons	3(6.3)	2(4.1)	3(2.8)	2(2.6)
Protocol deviation	5(10.4)	3(6.1)	4(3.7)	4(5.1)
Subject withdrew consent	11(22.9)	10(20.4)	11(10.2)	9(11.5)
Unsatisfactory compliance	3(6.3)	4(8.2)	7(6.5)	3(3.8)

- Note: For Specific Reasons of discontinuation, Percentages use number discontinued as denominator not all patients. Source: Tristan Massie, Ph.D., FDA statistical reviewer. This analysis is slightly different from the sponsor's analysis in page 37 of the ISS. Of note, subjects may have more than 1 reason for discontinuation. For this analysis the FDA statistician used the first reason for discontinuation.

There is a clear dose in terms of overall discontinuations (13.2%, 18.1%, 22.9% and 38.2% for placebo, LCM 200, LCM 400 and LCM 600, respectively). The most common cause of withdrawal was adverse events. Of the patients who withdrew from the LOCM 400 and LCM 600 groups, up to 75% did so because of an adverse event. Of the 41 subjects who had "consent withdrawal" indicated as their primary reason for discontinuation, seven subjects had an AE that

was ongoing at the time of discontinuation of the trial. The presence of an AE might have influenced the subject's decision to withdraw consent.

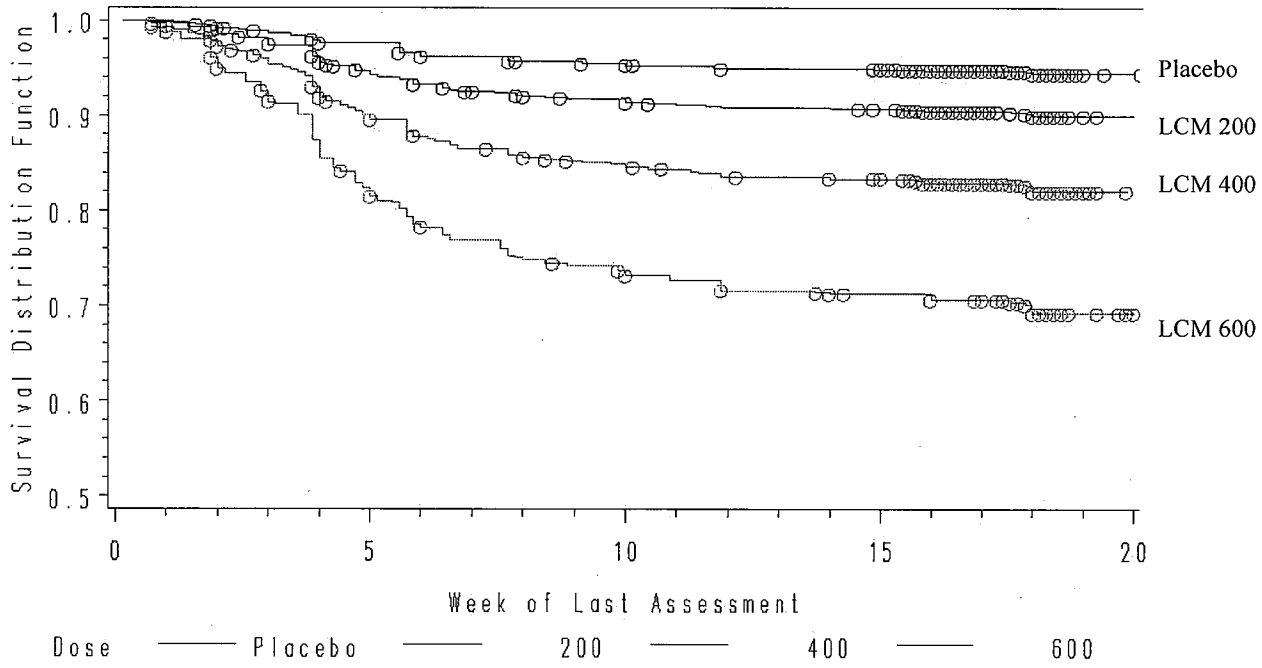
Despite the forced-titration dosing design (with permission of one-step dose reduction during the titration phase, prior to maintenance phase), the analyses by randomized dose show a clear dose response in terms of AE, particularly for discontinuations due to AE for the SOCs with the highest rates (Nervous System, Psychiatric and GI disorders).

7.4.2 Explorations for Predictive Factors

1) Explorations for time dependency for adverse findings

The following figure presents a Kaplan Mayer analysis of discontinuations (all causes) in the EP Pool 1. The most common cause of discontinuation was adverse events.

Figure 1. Kaplan Meier plot of Time to Discontinuation in Pool of Phase 3 Lacosamide Adjunctive Epilepsy Studies



Note: Circles on curves indicate week of last assessment for patients considered to be Completers or who Dropped out for non-AE related reason. Source: Tristan Massie, Ph.D., FDA statistical reviewer.

As seen in this figure, most dropouts occurred during titration, before week 4, although some continued to occur over time, in a dose-related manner.

2) Explorations for drug-demographic interactions

The available data do not suggests obvious drug-demographic interactions in terms of gender, age and race. However, the exposure of LCM in elderly and in non-Caucasia patients is limited in the epilepsy population (16 and 110, respectively, out of 944 in Pool EP S1). The sponsor has partially addressed this issue in clinical pharmacology studies, in young adult and elderly (SP 620) and males with different ethnicity (SP661). Additionally, there is some clinical data in elderly patients taking LCM for the DNP indication.

Regarding US versus non US populations, Tristan Massie, Ph.D. statistician, looked at the proportion of patients with Any AEs and Discontinuations due to AE for US and Foreign sites. Of note, study SP667 was 44% foreign and 56% domestic, SP754 was 100% domestic, and SP755 was 100% foreign. The odds of having no AEs was higher at non-US sites ($p<0.001$ 88% US vs. 58% non-US) (independent of treatment group). In study 667 which had both US and non-US sites the difference between US and non-US in odds of having no AEs was larger in the 0-200 dose range ($p=0.01$). Thus, it did depend somewhat on dose, i.e., at higher doses there was less difference between US and non-US sites in terms of the odds of having no AEs. Discontinuations due to AEs were affected by dose ($p<0.001$), independently of site location (US vs. non-US) (data not shown). An analysis of AE and dropouts due to AE by BMI show that more dropouts occurred in the LCM 600 dose in patients with lower BMI. This was not observed with other doses (**Appendix 24**)

3) Explorations for drug-disease interactions

This review focused on the epilepsy population only. This population was relatively healthy and did not include individuals with cardiac disease that may be of concern given the potential effects of LCM-in the heart conduction system.

2) Explorations for drug-drug interactions

No significant pharmacokinetic interactions were found in this database. However, one case of first degree AV block occurred in a healthy volunteer when LCM was added to digoxin in the digoxin interaction study (644/81002) and one case of symptomatic bradycardia with questionable AV block occurred in a patient who was on a beta blocker and received IV LCM. These cases support the concern that LCM needs to be used with caution in patients taking other drugs that prolong the PR interval.

An analysis of AEs by concomitant AED did not find significant differences.

b(4)

Table 93. Incidence of treatment emergent AE in subjects randomized to LCM in EP S1, by use of concomitant antiepileptic drugs (AED)

AED	% of LCM subjects using AED in study	% of AEs in users	% of AE in non users
Carbamazepine	35.4	77.5	83.0
Lamotrigine	30.8	80.9	81.4
Leviteracetam	29.4	88.1	78.1
Oxcarbazepine	17.3	87.7	79.6
Phenytoin	14.6	88.4	79.8
Topiramate	22.0	71.6	82.7
Valproate	22.6	70.9	84.0

This analysis shows that the rate of TEAE during LCM treatment was similar (or lower) for those patients taking concomitant carbamazepine, lamotrigine, topiramate and valproate as compared to those who were not, but was approximately 8-10% higher for those taking leviteracetam, oxcarbazepine and phenytoin, as compared to those who were not. The clinical significance of this observation is unclear.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing is a dose titration schedule, starting with 50 mg twice daily with weekly increases by 100 mg, up to a maintenance dose of 200 – — mg daily. The efficacy of this drug is being reviewed separately by Dr. Hershkowitz. It appears that there is a dose response in terms of efficacy, with a plateau effect at doses of 400 mg daily. Given the safety profile associated with the 600 mg/day dose (almost 40% required dose reduction and 30% required discontinuation due to adverse events, most events of syncope occurred at doses of ≥ 600 mg/day), it appears that the benefits do not outweigh the risks associated with LCM 600. I would recommend that the maximum recommended dose in labeling be 400 mg daily.

b(4)

8.2 Drug-Drug Interactions

No significant Clinical Pharmacology drug-drug PK interactions have been identified.

8.3 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).

Clinical Pharmacology studies in the elderly showed a 25% increased LCM exposure in the elderly as compared to non-elderly adults. This small increase is unlikely to be of clinical relevance, however, it does not rule out an increased risk of adverse events in elderly patients with concomitant renal, cardiac and other diseases, who were not studied in this database.

8.4 Pediatrics

LCM has not been studied in children and adolescents younger than 16 years. Few patients younger than 18 were studied in this database (n=7).

8.5 Advisory Committee Meeting

No AC meeting is planned at the time of this review.

8.6 Literature Review

There is no independent literature referring to LCM. All published information comes from the sponsor, based on studies conducted and submitted as part of this NDA.

8.7 Postmarketing Risk Management Plan b(4)

The sponsor proposes —— . I recommend — b(5)

9 OVERALL ASSESSMENT

9.1 Conclusions

Lacosamide is safe at doses of 200 to 400 mg daily. Doses of 600 mg daily are associated with increased toxicity and do not seem to provide additional benefit.

9.2 Recommendation on Regulatory Action

From the safety point of view, these applications may be Approved. If approved, the maximum recommended dose should be 400 mg daily and the intravenous formulation should be used as temporary replacement of the oral formulation in patients who are at a stable dose of oral LCM.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant proposes [redacted] to address the risk of PR prolongation and liver toxicity. The sponsor's proposal [redacted] b(4)

[redacted] Additional safety issues that may need to be addressed with a Risk Evaluation and Minimization Strategy (REMS) are suicidality, atrial arrhythmias, syncope, and potential multiorgan hypersensitivity reactions. There is evidence of a potential risk of drug abuse with LCM. This drug is recommended to be under Schedule IV of the Controlled Substance Act.

9.3.2 Required Phase 4 Commitments

Recommendations will be discussed in an addendum to this review.

9.3.3 Other Phase 4 Requests

Recommendations will be discussed in an addendum to this review.

9.4 Labeling Review

Draft labeling review will be submitted as an addendum to this review.

9.5 Comments to Applicant

Recommendations to the applicant will be submitted as an addendum to this review.

b(4)

10 APPENDICES

Appendix 1. Background information for the phase 2/3 studies for partial onset-seizures

- Design of the placebo-controlled studies

The placebo-controlled epilepsy studies included an 8-week baseline phase, a 4-6 forced up-titration period and a maintenance period (12 weeks for studies xx and xx, and 4 weeks for study xx), followed by a 2-3 week "transition"or "tapering" phase. In SP667, subjects randomized to LCM 200 and 400mg/day received placebo for 4 or 2 weeks, respectively, during dose titration. In SP755, subjects randomized to 200mg/day received placebo for 2 weeks during dose titration. In contrast, in SP754, subjects randomized to LCM (400 and 600mg/day) received active drug beginning at Week 1; subjects randomized to 400mg/day reached their target dose at Week 4 and continued to receive this dose for 2 additional weeks. Subjects who had been on LCM 600 and LCM 400 were tapered in 200 mg/day decrements; those subjects who had been treated with LCM 200 mg/day were discontinued without taper from that dose.

The starting dose in these trials was 50 mg bid, with forced up-titration up to 100 mg weekly, to the target (randomized) dose over 4 weeks (SP755) or 6 weeks (SP667 and SP754). However, a **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** (to 100 mg/day for SP667 and SP755; 300 mg/day for SP667, SP754, and SP755; and 500mg/day for SP667 and SP754). Subjects who required a second back titration were to be discontinued from the trials in order to reduce ambiguity among treatment groups.

A faster titration scheme was studied in 2 trials in subjects with partial-onset seizures (SP586 and SP598, which used the oral capsule formulation). In these 2 trials, subjects were started on a total daily dose of 200 mg/day (100mg 2 times a day) and escalated by 200 mg/day in weekly intervals. In these trials, LCM was less well tolerated and thus, the slower rate is currently recommended.

- Patient eligibility in phase 2/3 studies

Selection criteria included male or female subjects aged at least 16 years with a primary diagnosis of partial onset seizure for at least 2 years and were required to be taking between 1-3 approved antiepileptic drugs (AEDs), with or without concomitant vagal nerve stimulation (VNS). Subjects were required to have at least 4 partial-onset seizures per 28 days, on average.

Patient were excluded if they had

- Other type of seizures (generalized and unclassified) or other neurologic conditions other than epilepsy; status epilepticus; primary generalized seizure; seizures that were

uncountable due to clustering; nonepileptic events that could be confused with seizures; and progressive structural lesions in the CNS, or a progressive encephalopathy.

- A history of chronic alcohol or drug abuse within the previous 2 years.
- Any medical or psychiatric condition, which in the opinion of the investigator, could have jeopardized the subject's health or would have compromised the subject's ability to participate in this trial.
- Known hypersensitivity to any component of the investigational product(s) as stated in the protocol. Note: This was not exclusionary in SP667.
  - Pregnant or nursing women and/or those of childbearing potential with no adequate contraception.

4) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin level ≥2 times the upper limit of normal; a serum creatinine level ≥2 times the ULN (for SP667) or a creatinine clearance < 50mL/min at Visit 1 for SP754 and SP755.
5) **A diastolic blood pressure <50mmHg or >105mmHg or pulse less than 50beats per minute (bpm) or >110bpm, after 3 minutes in a sitting position. Subject with heart rate by ECG <50bpm or >110bpm. (Note: In SP667, subjects with sitting diastolic blood pressure <60mmHg or >105mmHg or resting pulse >45bpm or >110bpm were excluded.)**
6) **A confirmed clinically significant abnormality in ECG, including prolonged QTc (Bazett's machine-read) interval defined as ≥450ms for males and ≥470ms for females.**
7) A known history of severe anaphylactic reaction or serious blood dyscrasias.
8) Subject with concomitant treatment of felbamate or previous felbamate therapy within the 6 months prior to trial entry.
9) Subject had taken vigabatrin concomitantly (SP667, SP754, and SP755) or in the preceding 6 months (SP754 and SP755). Subjects with a history of vigabatrin treatment must have had a visual perimetry test following conclusion of the treatment.
10) Subject was taking 1 of the following medications influencing the CNS on a regular basis within 4 weeks prior to trial entry: neuroleptics, monoamine oxidase inhibitors, barbiturates (except for medication taken as concomitant anticonvulsant treatment), and narcotic analgesics. In addition, in SP667, use of the following medications taken within 4 weeks prior to trial entry was exclusionary: anxiolytics, amphetamines, sedative antihistamines, tranquilizers, and hypnotics.

- Selection of dose for placebo-controlled studies in partial-onset seizures: study SP607

SP607 was a Phase 2, multi-center, open-label, single-arm trial of oral tablet formulation LCM conducted to determine the maximum tolerated dose (MTD) of LCM 100 mg/day to 600 mg/day. In this study, after a 4-week observational baseline, the dose Titration began at 100mg/day for the first week (on a BID basis of 50mg a.m. and 50mg p.m.), and increased 100mg/day each

week (increases of 50mg a.m. and 50mg p.m.) until the maximum tolerated dose was achieved, up to 600mg/day. The maximum tolerated dose was defined as the maximum dose received for one week without the occurrence of adverse events causing dose-reduction or discontinuation. After a subject had tolerated their maximum dose, the subject continued the Maintenance Period for 4 additional weeks. Two dose-reduction steps were allowed; subjects who required more than two dose-reduction steps were withdrawn from the trial. The maximum duration of treatment recorded was 91 days (13 weeks).

- Safety results: The median MTD was 300mg/day. MTDs ranged from No Dose Tolerated (NDT) to 600mg/day. Approximately 25% of patients tolerated LCM 600 mg/day and approximately 50% of subjects had an MTD of 400 to 600mg/day.
- Efficacy results: The median change from baseline in seizure frequency across all subjects was –3.88 at maintenance endpoint (defined as last observation carried forward) corresponding to a median percent change of -31.81%. (There was no analysis of dose-response in terms of efficacy).
- Pharmacokinetics Results: The dose-dependent increase of the measured plasma concentration indicated dose-proportionality of LCM pharmacokinetics in these subjects. LCM did not appear to influence the plasma concentrations of other measured AEDs including carbamazepine (and the metabolite, epoxy-carbamazepine), the 10-hydroxy metabolite of oxcarbamazepine gabapentin, lamotrigine, phenytoin, zonisamide, and levetiracetam.

On the basis of these results, LCM 200mg/day, 400mg/day, and 600mg/day were investigated in 3 subsequent adequate and well-controlled trials.

- Phase 2/3 Open label studies

Example from study SP756 (OL extension to SP754). Subjects who complete the Maintenance and Transition Phases of the SP754 trial were allowed to enroll in this open-label extension trial. At the completion of the previous trial, subjects will be receiving LCM 200mg/day. At the beginning of the extension trial, the investigator may decrease the dose to 100mg/day or increase the dose no faster than 100mg/day per week up to 800mg/day. Subjects receiving between 400mg/day and 700mg/day SPM 927 may have their dose increased to the next level (ie, 100mg/day increase) only during a clinic visit. A decision to increase the dose to 800mg/day may be made only after the subject has taken a dose of 700mg/day for at least 1 week. Subjects receiving 700 or 800mg/day SPM 927 must return to the clinic for an unscheduled visit following their first week on that dose to ensure it is well tolerated.

During the trial, investigators were allowed to increase or decrease the dose of up to 3 concomitant AEDs and/or LCM to optimize tolerability and seizure reduction for each subject. If needed, to optimize tolerability and seizure reduction in selected subjects, the concomitant AED(s) could be carefully tapered and discontinued to achieve LCM monotherapy. New concomitant AEDs could be introduced as treatment if the medication had

been approved by the FDA. New AEDs could be added only when the subject had not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdrew from the trial, the trial medication should have been tapered off gradually at a recommended decrease rate of 200mg/day per week.

Appendix 2. IV LCM studies (source ISS and individual study reports)

- Single dose, phase 1 LCM intravenous infusion

SP834
The first trial of LCM in man evaluated the safety and tolerability of four single intravenous doses (50, 100, 150, 300mg) versus placebo in 28 healthy male subjects. Each dose was infused over a period of 10min in a group of 7 subjects (6-LCM, 1-placebo). The 300mg dose was administered in a volume of 30mL (10mg/mL); the lower doses were administered in a volume of 20mL (2.5-7.5mg/mL).

SP645 and SP658
Two trials in healthy male volunteers were conducted to assess the bioavailability of 200mg of LCM solution for infusion administered over 60min, over 30min, and over 15min versus oral administration of the same dose in a crossover design. Administration over 60min or 30min was bioequivalent, however administration of 200mg LCM over 15min met the bioequivalence criteria for AUC but just exceeded the criteria for Cmax (20 % above).

SP643
Randomized, tow-way crossover trial to investigate the PK and bioavailability of oral and IV LCM in poor and extensive metabolizers (CYP 2C19). PK analyses suggest that CYP 2C19 has no relevant effect on the metabolic fate of LCM.

Subject disposition for Phase 1 IV LCM trials in healthy subjects: All subjects treated with LCM in SP645 and SP834 completed their respective trial. One subject (8.3%) discontinued from SP643 due to an AE; this subject received IV LCM but discontinued prior to receiving oral LCM. Five subjects (18.5%) discontinued from SP658, 3 due to an AE and 2 due to "other" reasons. Of the subjects who discontinued from SP658, 1 discontinued after oral LCM, 3 discontinued after IV LCM 60-minute infusion, and 1 discontinued after IV LCM 30-minute infusion.

- **Phase 2/3 studies with LCM intravenous infusion**

Selection for inclusion

Selection of subjects at the investigator sites was based initially on the eligibility criteria provided in the protocol, as well as interest by the subject. To participate in either of the IV LCM trials, subjects were required to have been enrolled in the applicable open-label oral LCM trial and receiving oral LCM for at least 8 weeks, with a stable twice daily dosing regimen for the last 2 weeks. There were no additional criteria in place for the selection of subjects for the Phase 2/3 IV LCM trials.

SP616 was a multicenter, double-blind, double-dummy, randomized trial to investigate the safety, tolerability, and pharmacokinetics of IV LCM as replacement for oral LCM in subjects with partial-onset seizures with or without secondary generalization. A total of 60 subjects, who were participating in an open-label extension trial (SP615) of oral LCM, were enrolled from 7 sites in the USA and Lithuania. The subjects were randomized in a 2:1 ratio to iv LCM plus placebo tablets bid or IV placebo plus oral LCM bid, respectively. Subjects were enrolled into 1 of 2 cohorts (A and B). Subjects in Cohort A received 60-minute infusions of trial medication; whereas Cohort B received 30-minute infusions of trial medication. Enrolled subjects entered into a 1-day Screening Phase during which all subjects received a single infusion of IV placebo in a single-blind fashion. There was a 2-day Treatment Phase during which subjects received blinded trial medication twice daily. The dose of LCM (100 to 300mg bid) during SP616 was the same as the subject's current daily dose in the open-label extension trial of oral LCM. End of Trial Phase assessments were performed the day after the Treatment Phase was completed, after which subjects continued in the open-label extension trial (SP615). Fifty-nine of 60 randomized subjects completed SP616; the reason for premature discontinuation in a single subject was because the site staff had difficulty gaining venous access for PK sampling.

Few AEs were reported during the trial. A total of 8 subjects (27%) in Cohort A and 8 subjects (27%) in Cohort B reported at least 1 treatment-emergent AE. In general, the incidences of AEs were comparable between the cohorts and between the treatment groups. Events reported by 2 or more subjects in a treatment group/cohort included only injection site pain, dizziness, headache, back pain, and somnolence. All events were mild or moderate in intensity, and most were mild. No subjects died during this trial, and no serious AEs were reported. No subjects withdrew from the trial due to an adverse event. Evaluation of ECG data from this trial did not reveal any tendency for IV LCM to prolong the QT/QTc interval or cause associated effects on repolarization. The sponsor found no clear differences in mean PR, RR, or QRS intervals were noted among the treatment groups. A small increase in PR interval was observed in both treatment groups of both cohorts. **In my opinion, the data suggest a larger effect in the PR interval with the IV formulation.** Comprehensive laboratory evaluations as well as assessment of heart rate and systolic and diastolic blood pressure did not reveal any issues of clinical concern. There did not appear to be an increase in the daily number of seizures reported during SP616 compared with the period prior to entry into SP616.

SP757 was a multi-center, open-label, inpatient trial to investigate the safety and tolerability of IV LCM as replacement for oral LCM in subjects with partial-onset seizures with or without secondary generalization who were taking oral LCM chronically. The subjects enter into a 1-day Screening Phase followed by a 2- to 5-day Treatment Phase during which subjects receive iv LCM infused over 30, 15, or 10 minutes (depending on the cohort) twice daily (10 to 400 mg bid). The dose of LCM during SP757 was the same as the subject's current daily dose in the open-label extension trial of oral LCM. Only 3 ECGs are collected following each intravenous dose in SP757.

A total of 160 subjects were enrolled into 1 of 5 possible cohorts in this trial. This trial was designed to identify the appropriate infusion duration(s) for LCM as short-term replacement for oral LCM and to provide the data that will support the safety of that infusion duration. Execution of this trial design resulted in the administration of LCM at progressively faster infusion durations under the direction of a Data Monitoring Committee (DMC). Depending on the intra-trial findings, the trial planned to expose up

to 40 to 80 subjects to an infusion duration of 30 minutes, up to 40 to 100 subjects to an infusion duration of 15 minutes, and up to 20 subjects to an infusion duration of 10 minutes.

The majority of subjects in SP757 completed the trial (98%; 157 subjects). Three subjects (all in the 15-minute infusion duration group) prematurely discontinued from the trial due to AEs (2 subjects) or "other" reasons (1 subject). Disposition is presented in the following table.

Exposures by LCM dose for SP757

Total daily LCM dose (mg)	Subject exposures		
	10min infusion	15min infusion	30min infusion
	n (%)	n (%)	n (%)
200	2 (10%)	17 (17%)	5 (13%)
300	4 (20%)	18 (18%)	3 (8%)
400	7 (35%)	28 (28%)	13 (33%)
500	4 (20%)	11 (11%)	8 (20%)
600	3 (15%)	19 (19%)	11 (28%)
700	0	5 (5)	0
800	0	2 (2)	0
Total	**20**	**100**	**40**

LCM=lacosamide; min=minute
Data source: 5.3.5.2.7 EP: SP757 Table 9.1

Across all infusion duration groups, 111 subjects (69%) were taking a daily dose of LCM 400mg/day to LCM 800mg/day. In the 15-minute infusion duration group, 65 subjects (65%) were taking a daily dose of LCM 400mg/day to LCM 800mg/day; 26 subjects (26%) were taking LCM 600mg/day to LCM 800mg/day. Overall, 79 subjects (49%) were exposed to 4 or 5 days of IV LCM (all at the 15- or 10-minute infusion durations). 43%, 24%, and 35% of subjects reported AEs reported in the 30-, 15-, and 10-minute infusion duration groups, respectively. Across all infusion duration groups, treatment-emergent AEs were most common in the nervous system disorders system organ class (SOC). There were 33%, 12%, and 15% of subjects reporting at least 1 AE in the nervous system disorders SOC for 30-, 15-, and 10-minute infusion duration groups, respectively. Within the nervous system disorders SOC, headache and dizziness were the most common AEs reported during the Treatment Phase.

No subject died during the trial. There was 1 serious adverse event (SAE) reported during the trial. This SAE of bradycardia occurred during a 15-minute infusion on Day 2 of IV LCM but had not occurred the preceding day with 2 identical infusions. The investigator assessed the event as probably related to LCM. The subject was discontinued from this trial and returned to the open-label extension trial. One additional subject withdrew early from the trial, per protocol, due to an AE of ECG QT correct interval prolonged.

Evaluation of ECG data from this trial did not show any tendency for iv LCM to prolong the QT/QTc interval. No clear differences in mean PR or QRS intervals were noted among the infusion duration groups. A small increase in mean PR interval was observed in all infusion duration groups. Two subjects had asymptomatic, transient PR interval >250ms.

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Appendix 3. Lacosamide NDA. Patients with Treatment Emergent Serious AE in EP Pool S2 during treatment phase by modal dose

MedDRA System Organ Class Patients with at least one event	LCM (mg/day)							
	100 N=79 n (%)	200 N= 291 n (%)	300 N=155 n (%)	400 N=383 n (%)	500 N=149 n (%)	600 N=194 n (%)	>600 N=76 n (%)	Total LCM N= 1327 n (%)
Any system organ class	16 (20.3)	39 (13.4)	28 (18.1)	67 (17.5)	31 (20.8)	41 (21.1)	15 (19.7)	237 (17.9)
Blood and lymphatic system disorders	0	1(0.3)	0	0	0	1 (0.5)	0	2 (0.2)
Cardiac disorders	0	1 (0.3)	3 (1.9)	4 (1.0)	0	2 (1.0)	0	11 (0.8)
Congenital, familial and genetic disorders	0	0	0	0	1 (0.7)	0	0	1 (0.1)
Ear and labyrinth disorders	1 (1.3)	1 (0.3)	0	0	0	1 (0.5)	0	3 (0.2)
Endocrine	0	0	0	1 (0.3)	0	0	0	1 (0.1)
Eye disorders	1 (1.3)	1 (0.3)	0	0	0	0	0	2 (0.2)
Gastrointestinal disorders	3 (3.8)	4 (1.4)	1 (0.6)	2 (0.5)	4 (2.7)	6 (3.1)	0	20 (1.5)
General disorders and admin site condit.	0	4 (1.4)	0	3 (0.9)	1 (0.7)	6 (3.1)	0	14 (1.1)
Hepatobiliary disorders	1 (1.3)	1 (0.3)	0	1 (0.3)	2 (1.3)	0	0	5 (0.4)
Immune system disorders	0	0	0	0	1 (0.7)	0	0	1 (0.1)
Infections and infestations	1 (1.3)	2 (0.7)	0	7 (1.8)	2 (1.3)	3 (1.5)	1 (1.3)	16 (1.2)
Injury, poisoning and procedural complic.	2 (2.5)	4 (1.4)	6 (3.9)	12 (3.1)	4 (2.7)	10 (5.2)	3 (3.9)	41 (3.1)
Investigations	1 (1.3)	2 (0.7)	2 (1.3)	4 (1.0)	2 (1.3)	3 (1.5)	0	14 (1.1)
Metabolism and nutrition disorders	1 (1.3)	1 (0.3)	0	1 (0.3)	3 (2.0)	1 (0.5)	0	7 (0.5)
Musculoskeletal and connective tissue	0	1 (0.3)	2 (1.3)	1 (0.3)	2 (1.3)	2 (1.0)	1 (1.3)	9 (0.7)

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Neoplasm, malignant and unspecified	1 (1.3)	3 (1.0)	1 (0.6)	0	3 (2.0)	2 (1.)	1 (1.3)	
Nervous system disorder	7 (8.8)	16 (5.5)	7 (4.5)	31 (8.1)	10 (6.7)	14 (7.2)	10 (13.2)	
Pregnancy, puerperium and perinatal	0	1	0	0	0	0	0	11 (0.8)
Psychiatric disorders	3 (3.8)	2 (0.7)	7 (4.5)	7 (1.8)	4 (2.7)	6 (3.1)	0	95 (7.2)
Renal and urinary disorders	1 (1.3)	1 (0.3)	1 (0.6)	0	1 (0.7)	1 (0.5)	0	2 (0.2)
Reproductive system and breast disorders	0	2 (0.7)	0	1 (0.3)	2 (1.3)	1 (0.5)	0	29 (2.2)
Respiratory, thoracic and mediastinal dis.	1 (1.3)	1 (0.3)	0	2 (0.5)	0	7 (3.6)	1 (1.3)	5 (0.4)
Skin and subcutaneous tissue disorders	1 (1.3)	0	1 (0.6)	1 (0.3)	1 (0.7)	0	0	6 (0.5)
Social circumstances	0	0	0	1 (0.3)	0	0	0	12 (0.9)
Surgical and medical procedures	0	1 (0.3)	2 (1.3)	4 (1.0)	2 (1.3)	1 (0.5)	1 (1.3)	4 (0.3)
Vascular disorders	0	0	0	3 (0.8)	1 (0.7)	1 (0.5)	0	1 (0.1)
								11 (0.8)
								5 (0.4)

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 S2. Source: Sponsor Table, Summary of Clinical Safety. Table EP.6.25.2.

Appendix 4. SAE by PT in the Nervous System disorders SOC in EP Pool S2, during treatment phase by modal dose

MedDRA PT	LCM (mg/day)							
Patients with at least one event	100 (N=79) n (%)	200 (N= 291) n (%)	300 (N=155 n (%)	400 (N=383) n (%)	500 (N=149) n (%)	600 (N=194) n (%)	>600 (N=76) n (%)	LCM Total (N=1327) n (%)
Any	7 (8.9)	16 (5.5)	7 (4.5)	31 (8.1)	10 (6.7)	14 (7.2)	10 (13.2)	95 (7.2)
Convulsions	3 (3.8)	5 (1.7)	1	14 (3.7)	8 (5.4)	3 (1.5)	4 (5.3)	38 (2.9)
Status epilepticus	0	2	0	5 (1.3)	1	3 (1.5)	2 (2.6)	13 (1.0)
Epilepsy	0	1	1	5 (1.3)	0	1	0	8 (0.6)
Dizziness	1 (1.3)	2	1	1	0	1	1 (1.3)	6 (0.5)
Grand mal convulsion	1 (1.3)	0	1	2	0	0	1 (1.3)	5 (0.4)
TIA	0	0	1	0	0	2 (1.0)	0	3 (0.2)
Headache	0	1	0	1	0	1	0	3 (0.2)
Coordination abnormal	0	2	0	1	0	0	0	3 (0.2)
Complex partial seizures	1 (1.3)	1	0	0	0	0	1 (1.3)	3 (0.2)
Subarachnoid hemorrhage	0	0	0	1	0	1	0	2 (0.2)
Somnolence	1 (1.3)	0	0	0	0	1	0	2 (0.2)
Hemiparesis	0	0	0	0	0	1	1	2 (0.2)
Hydrocephalus	0	0	1	1	0	0	0	2 (0.2)
Nystagmus	0	2	0	0	0	0	0	2 (0.2)
Cerebral hemorrhage	0	0	0	0	0	0	1	1(0.1)
Intracraneal pressure increased	0	0	0	0	0	1	0	1(0.1)
Metabolic encephalopathy	0	0	0	0	0	1	0	1(0.1)
Monoparesis	0	0	0	0	0	1	0	1(0.1)

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 S2. Source: Sponsor Table, Summary of Clinical Safety. Table EP 6.25.2.

Convulsion was again the most frequent SAE.

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Appendix 5 SAE by PT in the Injury, Poisoning and Procedural complications in EP Pool S2, during treatment phase by modal dose

MedDRA PT	LCM (mg/day)							
Patients with at least one event	100 (N=79) n (%)	200 (N= 291) n (%)	300 (N=155 n (%)	400 (N=383) n (%)	500 (N=149) n (%)	600 (N=194) n (%)	>600 (N=76) n (%)	LCM Total (N=1327) n (%)
Any	2 (2.5)	0	6 (3.9)	12 (3.1)	4 (2.7)	1 (0.5)	0	41 (3.1)
Lower limb fracture	1	0	2 (1.3)	1	0	1	1	5 (0.4)
Head injury	0	0	0	1	1	0	1	3 (0.2)
Hand fracture	0	0	0	1	0	1	0	3 (0.2)
Subdural hematoma	0	0	1	1	0	1	0	3 (0.2)
Fall	0	0	0	1	0	1	0	2 (0.2)
Pelvic fracture	0	0	0	1	0	1	0	2 (0.2)
Upper limb fracture	0	0	0	1	0	1	0	2 (0.2)
Drug toxicity	0	0	1	1	0	1	0	2 (0.2)
Injury	0	0	0	0	0	1	0	1 (0.1)
Overdose	0	0	0	0	0	1	0	1 (0.1)
Pneumothorax traumatic	0	0	0	0	0	1	0	1 (0.1)
Post-traumatic pain	0	0	0	0	0	1	0	1 (0.1)
Rib fracture	0	0	0	0	0	1	0	1 (0.1)
Road traffic accident	0	0	0	0	0	1	0	1 (0.1)
Tibia fracture	0	0	0	0	0	1	0	1 (0.1)
Accidental overdose	0	0	0	0	1	0	0	1 (0.1)
Hip fracture	0	0	0	0	1	0	0	1 (0.1)
Medical device complication	0	0	0	0	1	0	0	1 (0.1)
Radius fracture	0	0	0	0	1	0	0	1 (0.1)
Thermal burn	0	0	0	0	1	0	0	1 (0.1)

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 S2. Source: Sponsor Table, Summary of Clinical Safety. Table EP 6.26.2.

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Appendix 6. SAE by PT in the Psychiatric disorders SOC in EP Pool S2, during treatment phase by modal dose.

MedDRA Psychiatric disorders System Organ Class Patients with at least one event	LCM (mg/day)							
	100 (N=79) n (%)	200 (N= 291) n (%)	300 (N=155 n (%)	400 (N=383) n (%)	500 (N=149) n (%)	600 (N=194) n (%)	>600 (N=76) n (%)	LCM Total (N=1327) n (%)
Any	3 (3.8)	2 (0.7)	7 (4.5)	7 (1.8)	4 (2.7)	6 (3.1)	0	29 (2.2)
Confusional state	0	0	2 (1.3)	0	1 (0.7)	2 (1.0)	0	5 (0.4)
Depression	1 (1.3)	0	0	2 (0.5)	0	1 (0.5)	0	4 (0.3)
Aggression	0	0	0	0	2 (1.3)	1 (0.5)	0	3 (0.2)
Psychotic disorder	0	0	0	2 (0.5)	1 (0.7)	0	0	3 (0.2)
Epileptic psychosis	0	0	2 (1.3)	0	1 (0.7)	0	0	3 (0.2)
Major depression	0	0	0	0	0	2 (1.0)	0	2 (0.2)
Hallucination, auditory	0	0	1 (0.6)	0	0	1 (0.5)	0	2 (0.2)
Suicide attempt	1 (1.3)	0	0	0	0	1 (0.5)	0	2 (0.2)
Hallucination, visual	0	0	0	0	0	1 (0.5)	0	1 (0.1)
Hallucination	0	0	0	0	1 (0.7)	0	0	1 (0.1)
Mental status changes	0	0	0	0	1 (0.7)	0	0	1 (0.1)
Abnormal behavior	0	0	0	1	0	0	0	1 (0.1)
Acute psychosis	0	0	0	1	0	0	0	1 (0.1)
Paranoia	0	0	0	1	0	0	0	1 (0.1)
Anxiety	0	0	1 (0.6)	0	0	0	0	1 (0.1)
Nightmare	0	0	1 (0.6)	0	0	0	0	1 (0.1)
Suicidal ideation	0	0	1 (0.6)	0	0	0	0	1 (0.1)

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 S2. Source: Sponsor Table, Summary of Clinical Safety. Table EP 6.25.2.

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Appendix 7. AE that led to dropout in SOC with incidence <1% in EP S1

MedDRA System Organ Class Preferred Term	Placebo (N=364) n (%)	Lacosamide 200mg/day (N=270) n (%)	Lacosamide 400mg/day (N=471) n (%)	Lacosamide 600mg/day (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)
NEUTROPENIA	0	2 (0.7)	0	0	2 (0.2)
THROMBOCYTOPENIA	0	0	1 (0.2)	0	1 (0.1)
CARDIAC DISORDERS	0	1 (0.4)	3 (0.6)	0	4 (0.4)
EXTRASYSTOLES	0	0	2 (0.4)	0	2 (0.2)
SINUS BRADYCARDIA	0	0	1 (0.2)	0	1 (0.1)
CARDIOMYOPATHY	0	1 (0.4)	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	0	3 (1.1)	5 (1.1)	5 (2.5)	13 (1.4)
VERTIGO	0	3 (1.1)	4 (0.8)	5 (2.5)	12 (1.3)
VESTIBULAR DISORDER	0	0	1 (0.2)	0	1 (0.1)
FEELING DRUNK	0	0	1 (0.2)	0	1 (0.1)
HEPATOBILIARY DISORDERS	0	0	1 (0.2)	1 (0.5)	2 (0.2)
JAUNDICE	0	0	0	1 (0.5)	1 (0.1)
BILE DUCT STONE	0	0	1 (0.2)	0	1 (0.1)
CHOLELITHIASIS	0	0	1 (0.2)	0	1 (0.1)
INFECTIONS AND INFESTATIONS	0	0	0	1 (0.5)	1 (0.1)
HEPATITIS C	0	0	0	1 (0.5)	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.4)	1 (0.2)	2 (1.0)	4 (0.4)
DRUG TOXICITY	0	0	0	2 (1.0)	2 (0.2)
POISONING	0	0	1 (0.2)	0	1 (0.1)
CONCUSSION	0	1 (0.4)	0	0	1 (0.1)

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Appendix 7. cont. AE that led to dropout in SOCs with incidence <1%, EP S1

METABOLISM AND NUTRITION DISORDERS	0	0	1 (0.2)	1 (0.5)	2 (0.2)
HYPONATRAEMIA	0	0	1 (0.2)	1 (0.5)	2 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.3)	1 (0.4)	1 (0.2)	3 (1.5)	5 (0.5)
JOINT RANGE OF MOTION DECREASED	0	0	0	1 (0.5)	1 (0.1)
MUSCULOSKELETAL DISCOMFORT	0	0	0	1 (0.5)	1 (0.1)
MYALGIA	0	0	0	1 (0.5)	1 (0.1)
MUSCLE SPASMS	0	0	1 (0.2)	0	1 (0.1)
PAIN IN EXTREMITY	1 (0.3)	1 (0.4)	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.3)	1 (0.4)	0	0	1 (0.1)
SMALL CELL LUNG CANCER STAGE UNSPECIFIED	0	1 (0.4)	0	0	1 (0.1)
OLIGODENDROGLIOMA	1 (0.3)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (0.2)	0	1 (0.1)
DYSPNOEA	0	0	1 (0.2)	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.5)	0	5 (1.1)	1 (0.5)	6 (0.6)
RASH	2 (0.5)	0	2 (0.4)	0	2 (0.2)
PRURITUS	0	0	0	1 (0.5)	1 (0.1)
HYPERHIDROSIS	0	0	1 (0.2)	0	1 (0.1)
NIGHT SWEATS	0	0	1 (0.2)	0	1 (0.1)
URTICARIA	0	0	1 (0.2)	0	1 (0.1)
VASCULAR DISORDERS	1 (0.3)	0	0	0	0
ISCHAEMIA	1 (0.3)	0	0	0	0

Appendix 8. Lacosamide NDA. Incidence of treatment emergent AEs that led to early discontinuation by SOC, in at least 0.1% of patients in any treatment group, by SOC, during the treatment phase in EP Pool S2, by dose at AE onset.

MedDRA System Organ Class	LCM (mg/day)							
	100 (N=1232) n (%)	200 (N= 1297) n (%)	300 (N=1164) n (%)	400 (N=1076) n (%)	500 (N=675) n (%)	600 (N=525) n (%)	>600 (N=208) n (%)	All LCM (N=1327) n (%)
Any system organ class	38 (2.9)	61 (4.7)	53 (4.6)	74 (6.9)	21 (3.1)	15 (2.9)	2 (1.0)	243 (18.3)
Blood and lymphatic system disorders	1 (0.1)	0	1 (0.1)	0	0	0	0	2 (0.2)
Cardiac disorders	2 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)	0	0	0	7 (0.5)
Ear and labyrinth disorders	2 (0.2)	5 (0.4)	5 (0.4)	3 (0.3)	0	0	0	15 (1.1)
Eye disorders	8 (0.6)	8 (0.6)	7 (0.6)	11 (1.0)	1 0.2)	1	0	34 (2.6)
Gastrointestinal disorders	6 (0.5)	9 (0.7)	2 (0.2)	13 (1.2)	3 (0.4)	1	0	34 (2.6)
General disorders and admin site condit.	4 (0.3)	4 (0.3)	6 (0.5)	6 (0.6)	4 (0.6)	0	1 (0.5)	24 (2.8)
Hepatobiliary disorders	1 (0.1)	0	0	0	0	1	0	2 (0.2)
Infections and infestations	1(0.1)	0	0	0	1 (0.2)	0	0	2 (0.2)
Injury, poisoning and procedural com.	0	3 (0.2)	1 (0.1)	4 (0.4)	1 (0.2)	1	1 (0.5)	11 (0.8)
Investigations	3 (0.2)	4 (0.3)	4 (0.3)	2 (0.2)	0	0	0	13 (1.0)
Metabolism and nutrition disorders	1 (0.1)	0	0	1 (0.1)	0	0	0	2 (0.2)
Musculoskeletal and connective tissue	2 (0.2)	3 (0.2)	1 (0.1)	1 (0.1)	1 (0.2)	0	0	7 (0.5)
Neoplasm, malignant and unspecified	0	3 (0.2)	0	0	1 (0.2)	1	0	5 (0.4)
Nervous system disorder	13 (1.0)	29 (2.2)	32 (2.7)	41 (3.8)	11 (1.6)	9 (1.7)	0	127 (9.6)

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Psychiatric disorders	5 (0.4)	6 (0.5)	2 (0.2)	7 (0.7)	2 (0.3)	3 (0.6)	0	25 (1.9)
Respiratory, thoracic and mediast. dis.	0	1 (0.1)	0	2 (0.2)	0	1	0	4 (0.3)
Skin and subcutaneous tissue disorders	1 (0.1)	3 (0.2)	1 (0.1)	4 (0.4)	0	0	0	9 (0.7)

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. Adverse events with a dose at onset of zero are not included in this table. Patients with AE with an incidence <0.1 in Total LCM group are not included in this table. n = Number of subjects who reported at least one event during treatment. % = Percent with respect to the number of subjects for whom the dose was administered during treatment. Source: Sponsor's Table EP 6.29.2.

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Appendix 9 Adverse events of interest in phase I studies.

Study	Description (n, gender)	Safety Results of Interest*
SP619	OL, R, SD, oral & IV (n=10 M)	None
SP657	OL, R, 2-way, crossover 200 mg oral tablet [redacted] (n=16 M)	None
SP658	OL, R,SD, 3-way cross., oral tablet or IV 200mg over 30 or 60 min (n=22 M)	1 withdrawn because of epiglottitis (unrelated). b(4)
SP645	OL, R, SD, 2-way cross.	1 First degree AV block. ID 10036, receiving 200 mg IV over 15 min, appeared 0.25 hours after dose, duration approx 24 hs.
SP600	OL, R, SD, 2-way crossover (24 M)	1 ALT elevation; 1 syncope (ID 12395 at 300 mg), 1 vasovagal response (ID12345);
SP835	DB, R, PC, SD oral ascending (n=27 M)	1 dizziness/headache/double vision/nausea. Unclear duration. No ECG changes.
SP587	OL, single ascending oral dose (n=16M)	12 paresthesia (mostly around mouth/tongue) at 600 and 800 mg. 3 euphoria (ID8016, 8007 & 8014) at doses 400-800 mg. 1 slight increase in BP and slight PQ prolongation without AE 2 ataxia (800 mg), 1 hypokinesia (400 mg).
SP836	DB, R, PC, 7-day oral ascending (n=21M)	1 First degree AV block 10 ↑ ALT (±↑AST) < 2x ULN, that came down within 3 days to 3 weeks after end of study 3 slurred speech at 800 mg (1 with ataxia)
SP588	DB, R, PC, Multiple dose (16 days), oral capsule ascending dose (n=33M) N=24 LCM/9 Plac. 300 or 500 mg once or twice daily.	13 hyposthesia, 9 rash, 8 pruritus, 8 diplopia, 4 dry mouth, 4 ↑BP (1 on placebo), 1 hepatitis 12 days after end of study at 400 mg (ID#8061) 1↑ ALT + LDH (ID#8065); 1↑ LDH alone (ID#8059) at 1000 mg; 1↑ CPK + AST (ID#8066) 2 euphoria (at 600 mg and 500 mg/d, respectively) & 4 of feeling drunk 1 ataxia, 3 tremor; 5 fasciculation (2 in subjects with tremor) at 500 -1000mg
SP834	DB, R, PC, single IV ascending 50-300 mg (n=28M, 26LCM/4 Placebo)	2 asymptomatic ECG changes (1 ↑ QRS, 1 ↑ PR with 300 mg dose). Transitory (15 min post dose) tendency towards slight PR interval prolongation in the 300 mg group. The lower dose was associated with a shortened PR interval.
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).	1 elderly subject on LCM withdrawn because of ↑ BP prior to multiple dose admin. 1 elderly subject on placebo withdrawn because of atrial fibrillation. Most common: headache & fatigue Higher AUC in female (because lower body weight)

b(4)

SP643	OL, R, 2-way crossover (CYP2c19) (n=??) oral & IV infusion	Common: numbness of lips, headache, fatigue. 1 ↑CPK, 1 ↑ALT (< 2xULN)
SP661	DB, R, PC, multiple oral 200 mg in male of different ethnicity. (n=?M)	4 mild/moderate increased ALT (±↑ AST/GGT) on LCM 400 mg
SP641	OL, sequential, SD in subjects with renal impairment (n=32 M&F)	1 AE of polyuria unresolved. Common AE: feces discolored, constipation & headache.
SP642	OL, 100mg BID x 4.5 days in subjects with hepatic impairment (12 M& 4F)	1 Syncope ("Circulatory failure") (ID#80204), on day 5, fasting, 4 hours post dosing after blood drawn for PK sampling. Recovered after 30 min lying down. BP before last dose 107/73; prior days 105/64-139/83 mmHg. No orthostatic measurements done. ECG normal before event, but not repeated after. 2 cases of hematuria during run-in period.
SP644	DB, PC, R crossover, digoxin interaction (?M)	1 asymptomatic First degree AV block (ID 81002): 36 M, 46 min after first dose of LCM 200mg (on digoxin), PQ/PR interval 1 hour after dosing was 241 msec; 4 min later 204 msc; 4 hrs later, 188 msec; insuing few days 209-222 msec. Resolved day 24. Mild PQ/PR prolongation when LCM administered with digoxin.
SP660	OL, single and multiple dose, interaction with metfromin ((?M)	1 case of euphoria
SP601	OL, R, multiple dose crossover, valproic acid interaction (n=16 M)	2 ↑ALT 1 asymptomatic First degree AVB on Day 10, pre-morning dose, and Day 17, pre, 2hs and 4 hs post dose. Recovered. 1 ↑ diastolic BP to 179 mmHg on Day 1, 2 hours post-dose, which continued x 5 days. Diastolic BP was OK but heart rate was 123 rpm (ID#8016). Attributed by the investigator to be related to "trial activities" rather than dosing of medication.
SP602	OL, multiple dose crossover, valproic acid interaction (n=16 M)	1 euphoria (ID# 8008); 3 gingival bleeding; 2 rigor; 2 pustular rash (ID# 8004 & 8005) 1 withdrawal because of hemorrhagic cystitis on day 20, on LCM monotherapy
Study	**Description (n, gender)**	**Safety Results of Interest***
SP603	OL, multiple dose, carbamazepine interaction (20M)	Several had sinus bradycardia at entry (n=8) 3 First degree AV block (ID#8015, on Day 6.9 & 10, had sinus brady at entry; ID8002 on Day 9; ID#8012 on day 17). It was concluded that first degree AVB can be seen in healthy people and it was not clinically relevant. b(5)
SP618	OL, multiple dose, carbamazepine (CBZ) interaction (n=20 M)	2 cases of euphoria (ID#8011, on day 7, after first LCM dose; ID#8008, on day 15, after first LCM dose) considered possibly related to LCM (subjects were already taking CBZ). 1 subject withdrawn because of rash Several ↑ ALT < 2x ULN (± ↑AST, ↑GGT or ↑CK)
SP863	OL multiple dose, omeprazole interaction ((?M)	1 withdrawn because asymptomatic T wave inversion on LCM 100mg on Day 3 (considered by investigator possible related; resolved); 2 ↑ CPK attributed to exercise. 2 rashes probably not related to LCM. Tendency to slight ↑ QRS and heart rate observed during multiple dose LCM. PQ/PR values >200 msec (first degree AVB was seen in 5 subjects at pre-dose measures.

SP599	OL, oral capsule, Mycrogynon® interaction in 40 F	1 withdrawn because of "feverish infection" had cold symptoms at entry; 1 withdrawn because eosinophilia (no eos. at baseline but 16.#% on Day 1 of cycle 2; asymptomatic. On FU she still had eosinophilia. 7 subjects developed skin reactions: erythema, exanthema, itching, pruritus, pustular rash, rosacea & dry skin. 1 subject had ↑CK on day 1 and 13 of cycle 2 (up to 8x ULN), with ↑ AST, ALT &LDH. Subject is a body builder.
SP903	DB, R, single site, SD crossover, oral tablet evaluating abuse potential (n=76 M&F)	Most AE at the 800 mg/day dose: GI, Psych, ear & labyrinth disorders. Mild-mod euphoric mood was reported in 2.9% of patients on placebo, 2.9% of subjects on LCM 200 mg, 14.7% of subjects on LCM 800mg, 11.8% of subjectes on ALprazolam 1.5 mg, and 9.1% of subjectes on alprazolam 3 mg.
SP640	DB, single site, R, PC. Thorough QTc (M&F). LCM400 (n=60), LCM 800 (n=71), placebo (N=62), moxif (n=54)	1 rash at 400 mg; 1 spontaneous abortion 9 days after end of LCM 800 mg 1 withdrawn because of syncope followed by dizziness, abd pain and hematemesis, diagnosed as Mallory-Weiss tear (LCM 800 mg). See Text. 11 subjects withdrew consent from the 800 mg dose, and had an AE at the time of dc.

1. Most common AE in the Phase 1 studies (all in healthy subjects) were paresthesia (mostly around the mouth and tongue), hyposthesia, dizziness, headache and fatigue. ECG and vital signs were unremarkable, unless noted otherwise. Source Study synopses, Summary of clinical safety.

b(4)

Appendix 10. Common AE by SOC, treatment phase, by titration or maintenance in EP Pool S1, by randomization dose.

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	Ti	194 (53)	139 (51)	329 (70)	178 (88)	645 (68)
	M	150 (45)	135 (55)	245 (62)	90 (63)	470 (60)
	both	235 (65)	188 (70)	387 (82)	190 (93)	765 (81)
Ear and labyrinth disorders	Ti	8 (2)	11 (4)	25 (5)	11 (5)	47 (5)
	M	5 (1)	9 (4)	12 (3)	2 (1)	22 (3)
	both	13 (4)	15 (6)	33 (7)	13 (7)	61 (7)
Eye disorders	Ti	12 (3)	20 (7)	74 (16)	64 (32)	158 (17)
	M	10 (3)	17 (7)	35 (9)	8 (6)	60 (8)
	both	21 (6)	30 (11)	97 (21)	68 (34)	195 (21)
Gastrointestinal disorders	Ti	36 (10)	44 (16)	99 (21)	63 (31)	206 (22)
	M	27 (8)	27 (11)	56 (14)	18 (13)	101 (13)
	total	53 (15)	57 (21)	127 (27)	75 (37)	259 (27)
General disorders and admin site condit.	Ti	38 (11)	29 (11)	72 (15)	46 (23)	147 (16)
	M	12 (4)	15 (6)	26 (7)	16 (11)	57 (7)
	total	49 (14)	40 (15)	89 (19)	57 (29)	186 (20)
Infections and infestations	Ti	34 (9)	26 (10)	47 (10)	23 (11)	96 (10)
	M	47 (14)	40 (16)	66 (17)	20 (14)	126 (16)
	total	69 (19)	59 (22)	102 (22)	38 (20)	198 (21)
Injury, poisoning and procedural complic.	Ti	19 (5)	11 (4)	32 (7)	17 (8)	60 (6)
	M	19 (6)	19 (8)	46 (12)	13 (9)	78 (10)
	total	32 (10)	26 (10)	73 (16)	26 (13)	125 (13)

b(4)

Investigations	Ti	12 (3)	16 (6)	32 (7)	25 (12)	73 (8)
	M	11 (3)	12 (5)	26 (7)	9 (6)	47 (6)
	total	22 (6)	26 (10)	54 (12)	32 (16)	112 (12)
Metabolism and nutrition disorders	Ti	6 (2)	6 (2)	17 (4)	8 (4)	31 (3)
	M	1 (<1)	7 (3)	9 (2)	3 (2)	19 (2)
	total	7 (2)	12 (4)	25 (5)	11 (5)	48 (5)
Musculoskeletal and connective tissue dis.	Ti	19 (6)	10 (4)	27 (6)	17 (8)	54 (6)
	M	19 (6)	17 (7)	27 (7)	15 (11)	59 (8)
	total	35 (10)	25 (9)	48 (10)	27 (13)	100 (10.6)
Nervous system disorders	Ti	94 (26)	64 (24)	216 (46)	131 (65)	411 (44)
	M	49 (15)	55 (22)	96 (24)	45 (32)	196 (25)
	total	121 (33)	99 (37)	257 (55)	147 (72)	503 (53)
Psychiatric disorders	Ti	20 (6)	10 (4)	45 (10)	24 (12)	79 (8)
	M	9 (3)	13 (5)	29 (7)	7 (5)	49 (6)
	total	26 (7)	22 (8)	69 (15)	30 (15)	121 (13)
Respiratory, thoracic and mediastinal dis.	Ti	15 (4)	9 (3)	31 (7)	15 (7)	55 (6)
	M	15 (4)	13 (5)	20 (5)	9 (6)	42 (5)
	total	27 (7)	20 (7)	49 (10)	20 (10)	89 (9)
Skin & SC tissue disorders	Ti	22 (6)	14 (5)	31 (7)	19 (9)	64 (7)
	M	13 (4)	11 (4)	25 (6)	6 (4)	42 (5)
	total	33 (9)	23 (9)	51 (11)	23 (11)	97 (10)

Note: Treatment Phase includes both Titration and Maintenance Phase data. Note: n = Number of subjects who reported at least one event during the phase. Percentages for the subgroup category are calculated with respect to the number of subjects in Pool S1. Of note, given the fact that some patients discontinued from the titration phase, the number of patients who received at least one dose during maintenance phase was 337 for placebo, 246 for LCM 200 mg/day; 393 for LCM 400mg/day and 142 for LCM 600 mg/day. Source: Tables 6.17.1, 6.18.1 and 6.1.1, ISS.