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.

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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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