Appendix 11a. Cases of dyskinesia in partial onset seizure studies (EP S1)

ID	Age/ gender	Trtgroup	AE term	Action	Outcome	Rel day	AE dose
754012311	58 M	Placebo	intermittent jerking right extremities	not changed	R	13	0
667010114	36F	LCM 400	muscle jerks in hands	not changed	R	2	0
754011403	40F	LCM 400	left arm jerking	not changed	R	23	400
754012407	51F	LCM 400	hand jerks/intermittent dizziness & balance problems	not changed	R	24	400
755110405	29M	LCM 400	dyskinesia, intermittent	not changed	R	94	100 & 400
754012605	26M	LCM 600	worsened rapid rhythmic movement/intention tremor	drug interrupted	R	64	500

Source: AE EP S1Database submitted January 2008

Appendix 11.b. Listing of patients with dyskinesia during open label epilepsy studies (EP S2)

ID	Age /gender	AE term	Action	Outcome	Rel st day	AE dose
607001011	44 F	Jerking in shoulders and arms	not changed	No R	1785	600
607001002	30 F	Hands jerking	not changed	No R	6	100
667011803	46F	Bilateral arm /hand jerks (intermittent)	not changed	R	459	600
667012410	26M	Jerking of hands and arms	not changed	R	927	700
667018805	61F	jerks	not changed	No R	789	700
754011801	25 M	Decreased rapid rhythmic movement R side/ decreased had swing R side./ Abnormal coordination, dizziness, increased seizure activity, tremor.	not changed	R	422	600
754012602	35F	intermittent limb jerking	not changed	No R	651	600
754015105	62 F	jerkiness	not changed	No R	145	300
754016005	47M	Arm and leg jerking (at night)/ hand tremor, unsteadiness	Dose reduced	R	571	500
755124605	22M	Jerky	not changed	R	302	400

Source: AE datasets. EP S2. Safety Update Report. January 2008.

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Appendix 12. Standard laboratory assessments and laboratory values considered to be outside the normal range in this application.

Laboratory parameter unit	Conversion	Markedly abnormal criteria
Clinical chemistry		
Albumin (g/dL)	(g/L) / 10	≤2.6
Alkaline phosphatase (U/L)	NA	≥3xULN
Bicarbonate (mEq/L)	mmol/L	<18, >38[a]
Bilirubin, total (mg/dL)	NA	≥2.0
BUN (mg/dL)	(mmol/L) / 0.357	≥40
Calcium (mg/dL)	NA	≤7.6, ≥11.0
Cholesterol (mg/dL)	(mmol/L) / 0.026	>250
Creatinine (mg/dL)	NA	≥2
GGT (U/L)	NA	≥3xULN
Glucose (mg/dL)	NA	<50, ≥200[a] <50, ≥250[b]
Phosphorus (mg/dL)	NA	≤2.0, ≥6.0
Potassium (mEq/L)	mmol/L	≤3.0, ≥6.0
AST (U/L)	NA	≥3.0xULN; ≥5.0xULN; ≥10.0xULN
ALT (U/L)	NA	≥3.0xULN; ≥5.0xULN; ≥10.0xULN
Sodium (mEq/L)	mmol/L	<127, >151
Uric Acid (mg/dL)	(umol/L) / 59.48	>9.5
Chloride (mEq/L)	mmol/L	≤90, ≥112
Hematology		
Hematocrit (%)	NA	≤85% of LLN; ≥15% of ULN
Hemoglobin (g/L)	NA	≤85% of LLN; ≥15% of ULN
WBC count (G/L)	NA	≤3.0, ≥16.0
Lymphocytes absolute (G/L)	NA	<0.6, >5.0

Appendix 13. Median changes in hematology parameters during the treatment phase in EP S1

	Placebo N=364		LCM 200mg/day N=270		LCM 400mg/day N=471		LCM 600mg/day N=203	
Hematology parameter (unit)	**n**	**median**	**n**	**median**	**n**	**median**	**n**	**median**
RBC count (T/L)								
Baseline[a]	363	4.5	270	4.5	471	4.5	203	4.4
Change End of MP[b]	320	0.00	217	0.00	362	0.00	122	0.00
Min change Post-Baseline[c]	355	-0.20	267	-0.20	468	-0.20	201	-0.20
Max change Post-Baseline[c]	355	0.10	267	0.10	468	0.20	201	0.10
Hematocrit (%)								
Baseline[a]	363	41.2	270	42.0	471	41.8	203	41.2
Change End of MP[b]	317	0.00	215	0.00	359	0.00	122	-0.55
Min change Post-Baseline[c]	355	-2.00	267	-2.00	468	-1.40	201	-2.00
Max change Post-Baseline[c]	355	1.00	267	1.20	468	1.40	201	1.10
Hemoglobin (g/L)								
Baseline[a]	363	140.0	270	141.0	471	141.0	203	139.0
Change End of MP[b]	320	-0.50	217	-1.00	362	0.00	122	-1.00
Min change Post-Baseline[c]	355	-6.00	267	-6.00	468	-5.00	201	-6.00
Max change Post-Baseline[c]	355	4.00	267	4.00	468	5.00	201	4.00
WBC count (G/L)								
Baseline[a]	363	5.8	270	5.7	471	6.0	203	5.6
Change End of MP[b]	320	0.10	217	0.10	362	-0.20	122	-0.20
Min change Post-Baseline[c]	355	-0.70	267	-0.70	468	-0.80	201	-0.70
Max change Post-Baseline[c]	355	1.10	267	1.00	468	0.80	201	0.80
Neutrophils absolute (G/L)								
Baseline[a]	363	3.46	270	3.26	471	3.54	203	3.25
Change End of MP[b]	318	0.00	216	0.09	359	-0.10	122	-0.12
Min change Post-Baseline[c]	355	-0.70	266	-0.56	468	-0.68	201	-0.54
Max change Post-Baseline[c]	355	0.94	266	0.90	468	0.75	201	0.75

Source: Sponsor's table in page 467 of ISS.

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Appendix 14.a. Marked hematologic abnormalities in EP S1 and EP S2

Laboratory parameter (unit)/criteria	Placebo N=364	LCM Total EP Pool S1 N=944	LCM Total EP Pool S2 N=1327
	n/N (%)	n/N (%)	n/N (%)
Hematocrit (%)			
≤0.85 LLN	5/354 (1.4)	11/932 (1.2)	24/1310 (1.8)
≥1.15 ULN	1/355 (0.3)	0/936	0/1315
Hemoglobin (g/L)			
≤0.85 LLN	5/354 (1.4)	6/930 (0.6)	21/1308 (1.6)
≥1.15 ULN	1/355 (0.3)	0/936	0/1315
WBC count (G/L)			
≤3.0	8/351 (2.3)	28/923 (3.0)	51/1297 (3.9)
≥16.0	3/355 (0.8)	2/933 (0.2)	9/1314 (0.7)
Neutrophils absolute (G/L)			
≤1.5	16/347 (4.6)	34/906 (3.8)	79/1274 (6.2)
Eosinophils absolute (G/L)			
≥1.0	1/352 (0.3)	4/930 (0.4)	13/1307 (1.0)
Eosinophils (%)			
≥10	6/349 (1.7)	21/922 (2.3)	46/1295 (3.6)
Platelet count (G/L)			
≤100	1/355 (0.3)	3/932 (0.3)	6/1310 (0.5)
≥600	1/355 (0.3)	2/933 (0.2)	7/1312 (0.5)

LCM=lacosamide; LLN=lower limit of normal; ULN=upper limit of normal; WBC=white blood cell
Note: Incidence=n of events/N at risk, where: n of events=number of subjects reporting the abnormality after start of treatment and did not report the reading before start of treatment, and N at risk=number of subjects with readings before and after start of treatment who did not report the abnormality before treatment. Assessment of marked abnormalities was based on all reported values (including unscheduled visits) during treatment.

Appendix 14.b. Marked abnormalities in hematologic parameters SP616

Table EP.11.2.1
Subjects with Marked Abnormalities for Hematology
Population: Trial SP616 SS

Cohort Treatment	Parameter: Markedly Abnormal Value	Site Number / Subject Number
A (60min) IV Lacosamide/ Oral Placebo	WBC: <=3.0 G/l	106/10526##
	Neutrophils Abs: <1.5 G/l	106/10526##
B (30min) Oral Lacosamide/ IV Placebo	Eosinophils: >=10 %	269/11506#
	Neutrophils Abs: <1.5 G/l	008/10194#, 268/11493#
IV Lacosamide/ Oral Placebo	Neutrophils Abs: <1.5 G/l	268/11467*, 269/11514##, 269/11524##

* only at baseline; # both, baseline and FU. ## Treatment emergent

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Appendix 14.c. Marked abnormalities in hematology values in SP757

Table 11.4.1
Subjects with Markedly Abnormal Hematology Values
Population: Safety Set

Infusion Duration (Cohort)	Parameter: Markedly Abnormal Value	Site Number / Subject Number
30-minute (Cohort A1)	Hemoglobin: <=85% of LLN	310/131001*
	WBC: <=3.0 G/l	308/130805*, 400/140001*
	Neutrophils Abs: <1.5 G/l	308/130805*, 310/131001#, 400/140001*
15-minute (Cohort B1)	Hemoglobin: <=85% of LLN	500/150004##
	Eosinophils: >=10 %	400/140013*
	Neutrophils Abs: <1.5 G/l	400/140016##
15-minute (Cohort B2)	Hematocrit: <=85% of LLN	308/130808#
	Hemoglobin: <=85% of LLN	308/130808#
	WBC: <=3.0 G/l	317/131702*, 400/140021*
	Eosinophils: >=10 %	600/160002#
	Monocytes: >=20 %	317/131702*
	Platelet Count: <=100 G/l	328/132802#
15-minute (Cohort B2)	Neutrophils Abs: <1.5 G/l	317/131702#, 328/132802*, 400/140021*, 701/170107##
10-minute (Cohort C)	WBC: <=3.0 G/l	500/150011*
	Neutrophils Abs: <1.5 G/l	500/150011*

Note: * = Abnormality only at Baseline. # = Abnormality at both Baseline and EOTP.
= Abnormality at EOTP but not at Baseline (Treatment-emergent).

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Appendix 15a. Marked abnormalities in chemistries in EP S1

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 (%)
Calcium (mg/dL)					
≤7.6	2/356 (0.6)	0/266	1/467 (0.2)	2/203 (1.0)	3/936 (0.3)
≥11.0	3/354 (0.8)	1/267 (0.4)	3/468 (0.6)	0/203	4/938 (0.4)
Chloride (mmol/L)					
≤90	8/352 (2.3)	6/264 (2.3)	7/464 (1.5)	3/200 (1.5)	16/928 (1.7)
≥112	24/339 (7.1)	11/247 (4.5)	27/431 (6.3)	7/195 (3.6)	45/873 (5.2)
Phosphorus (mg/dL)					
≤2.0	6/353 (1.7)	3/267 (1.1)	5/462 (1.1)	2/199 (1.0)	10/928 (1.1)
≥6.0	1/356 (0.3)	2/268 (0.7)	2/468 (0.4)	0/203	4/939 (0.4)
Potassium (mmol/L)					
≤3.0	0/355	0/268	0/467	0/202	0/937
≥6.0	2/354 (0.6)	3/267 (1.1)	6/467 (1.3)	2/203 (1.0)	11/937 (1.2)
Sodium (mmol/L)					
<127	8/353 (2.3)	3/262 (1.1)	7/466 (1.5)	3/199 (1.5)	13/927 (1.4)
>151	0/356	0/268	1/468 (0.2)	0/203	1/939 (0.1)
Glucose (nonfasting) (mg/dL)					
<50	4/352 (1.1)	3/263 (1.1)	9/467 (1.9)	1/202 (0.5)	13/932 (1.4)
≥200	0/351	0/266	5/465 (1.1)	0/201	5/932 (0.5)
Total cholesterol (mmol/L)					
>6.5	22/289 (7.6)	26/220 (11.8)	44/387 (11.4)	17/172 (9.9)	87/779 (11.2)
Uric acid (µmol/L)					
>565.06	3/355 (0.8)	3/268 (1.1)	3/468 (0.6)	0/203	6/939 (0.6)
Total bilirubin (mg/dL)					
≥2.0	0/356	0/267	0/468	0/203	0/938
Total bilirubin (mg/dL) and ALT (U/L)					
≥2.0mg/dL and ≥3xULN	0/356	0/266	0/466	0/202	0/934
Alkaline phosphatase (U/L)					
≥3xULN	0/355	0/268	0/468	0/203	0/939
GGT (U/L)					
≥3xULN	6/311 (1.8)	5/242 (2.1)	13/424 (3.1)	8/190 (4.2)	26/856 (3.0)
Albumin (g/L)					
<26	0/356	0/268	0/468	0/203	0/939
BUN (mmol/L)					
≥14.28	0/356	0/268	1/468 (0.2)	0/203	1/939 (0.1)
Creatinine (mg/dL)					
≥2.0	0/355	1/268 (0.4)	2/467 (0.4)	0/203	3/938 (0.3)
Bicarbonate (mmol/L)					
<18	16/346 (4.6)	9/259 (3.5)	27/459 (5.9)	8/196 (4.1)	44/914 (4.8)
>38	0/356	0/267	0/468	0/203	0/938

GGT=gamma-glutamyltransferase; LCM=lacosamide; LLN=lower limit of normal; ULN=upper limit of normal: Incidence=n of events/N at risk, where: n of events=number of subjects reporting the abnormality after start of treatment and did not report the reading before start of treatment, and N at risk=number of subjects with readings before and after start of treatment who did not report the abnormality before treatment.Assessment of marked abnormalities was based on all reported values (including unscheduled visits) during the Treatment Phase. Source: Sponsor's table pg 543 ISS.

Appendix 15b. Abnormalities in TG levels in EP S1

Incidence of Treatment Emergent Marked Abnormalities During the Treatment Phase - Triglycerides
Population: Pool S1

Lab Parameter Timepoint	Placebo (N=364) n/N (%)	Lacosamide 200mg/day (N=270) n/N (%)	Lacosamide 400mg/day (N=471) n/N (%)	Lacosamide 600mg/day (N=203) n/N (%)	Total (N=1309) n/N (%)
Triglycerides (mmol/l) - [>=1.5xULN]					
Titration	10/341 (2.9)	10/258 (3.9)	14/455 (3.1)	1/190 (0.5)	35/1244 (2.8)
Maintenance	4/323 (1.2)	4/234 (1.7)	13/392 (3.4)	4/132 (3.0)	25/1071 (2.3)
Treatment	11/341 (3.2)	10/258 (3.9)	21/455 (4.6)	4/190 (2.1)	46/1244 (3.7)

Appendix 15c. Marked abnormal chemistries in SP616

Table SP.11.2.2
Subjects with Marked Abnormalities for Clinical Chemistry
Population: Trial SP616 SS

Cohort Treatment	Parameter: Markedly Abnormal Value	Site Number / Subject Number
A (60min)		
Oral Lacosamide/ IV Placebo	GGT: >=3 x ULN	106/10540‡, 106/10545‡
	Cholesterol: >6.5 mmol/l	106/10533‡
IV Lacosamide/ Oral Placebo	GGT: >=3 x ULN	106/10531‡, 106/10536‡
	Cholesterol: >6.5 mmol/l	008/10176‡, 106/10531*, 118/10831‡‡
B (30min)		
Oral Lacosamide/ IV Placebo	GGT: >=3 x ULN	118/10834‡
	Cholesterol: >6.5 mmol/l	106/10547‡‡
	Uric Acid: >565.06 µmol/l	106/10547‡‡
B (30min)		
IV Lacosamide/ Oral Placebo	GGT: >=3 x ULN	106/12126‡
	Bicarbonate: <18.0 mmol/l	008/10191*
	Calcium: <=7.6 mg/dl	003/10061*
	Chloride: >=112 mmol/l	008/10191‡, 268/11488‡‡
	Glucose: >=200 mg/dl	003/10064‡
	Cholesterol: >6.5 mmol/l	268/11492*

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Appendix 15d. Marked chemistry abnormalities in SP757

Table 11.4.2
Subjects with Markedly Abnormal Clinical Chemistry Values
Population: Safety Set

Infusion Duration (Cohort)	Parameter: Markedly Abnormal Value	Site Number / Subject Number
30-minute (Cohort A1)	ALT: >=3 x ULN	500/150001##
	GGT: >=3 x ULN	500/150001#
	Bicarbonate: <18.0 mmol/l	308/130802*, 310/131001*, 400/140008##
	Chloride: >=112 mmol/l	300/130003*, 300/130004#, 400/140008##
	Phosphorus: <=2.0 mg/dl	302/130205##, 400/140002*
	Glucose: <50 mg/dl	308/130802##
	Cholesterol: >6.5 mmol/l	302/130201*, 400/140004#, 401/140101#, 401/140102##
15-minute (Cohort B1)	GGT: >=3 x ULN	304/130401#
	Bicarbonate: <18.0 mmol/l	401/140111*
	Chloride: >=112 mmol/l	401/140109*, 401/140111*, 401/140113##
	Glucose: >=200 mg/dl	401/140113##
15-minute (Cohort B1)	Cholesterol: >6.5 mmol/l	302/130212*, 400/140017#, 500/150003#, 500/150004#, 500/150009*, 500/150010##
15-minute (Cohort B2)	GGT: >=3 x ULN	301/130105#, 701/170109#
	Phosphorus: <=2.0 mg/dl	317/131701*
	Glucose: <50 mg/dl	314/131402##
	Cholesterol: >6.5 mmol/l	323/132304#, 323/132307#, 400/140021#, 401/140122*, 402/140202#, 600/160004#, 601/160102#, 701/170101#, 701/170103#, 701/170104#
10-minute (Cohort C)	GGT: >=3 x ULN	301/130101#, 325/132501#
	Chloride: <=90 mmol/l	304/130405*
	Sodium: <127 mmol/l	304/130405*
	Cholesterol: >6.5 mmol/l	500/150012#

Treatment emergent

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Appendix 16. Measures of central tendency for vital signs in EP S1.

Vital sign measurements during the Treatment Phase in subjects with partial-onset seizures (EP Pool S1)

Parameter (unit) 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
SBP (mmHg)												
Baseline[a]	364	121.9	13.74	270	121.5	13.33	471	120.8	13.54	203	122.2	14.84
Change End of TP	339	0.4	12.36	250	-0.3	11.66	412	1.3	12.34	157	2.4	12.20
Change End of MP[b]	323	0.1	12.29	225	1.0	11.59	366	1.2	13.04	127	-0.3	14.79
Min change Post-Baseline[c]	360	-8.7	10.65	268	-8.8	10.72	470	-8.1	10.87	203	-8.9	12.73
Max change Post-Baseline[c]	360	10.1	11.90	268	9.5	10.54	470	10.3	12.25	203	11.7	12.08
DBP (mmHg)												
Baseline[a]	364	76.4	8.83	270	76.5	8.99	471	76.1	9.42	203	76.3	8.73
Change End of TP	339	0.1	8.12	250	0.0	8.27	412	1.1	9.12	157	1.6	8.63
Change End of MP[b]	323	-0.4	8.94	225	1.1	8.54	366	0.6	9.26	127	1.1	9.06
Min change Post-Baseline[c]	360	-6.7	7.35	268	-6.4	7.79	470	-6.0	7.86	203	-5.8	7.69
Max change Post-Baseline[c]	360	6.7	7.73	268	7.1	7.24	470	7.1	8.17	203	8.8	7.98
Pulse rate (bpm)												
Baseline[a]	364	71.9	10.29	270	71.2	9.39	471	72.5	10.09	203	73.0	9.75
Change End of TP	339	0.6	9.93	250	1.8	9.18	412	1.1	9.14	157	1.5	9.46
Change End of MP[b]	323	0.8	9.98	225	0.9	10.17	365	0.7	10.04	127	0.4	10.41
Min change Post-Baseline[c]	360	-6.2	8.10	268	-5.2	8.16	470	-5.6	8.66	203	-6.5	8.06
Max change Post-Baseline[c]	360	8.7	8.92	268	9.0	9.04	470	8.3	8.84	203	9.5	9.41

bpm=beats per minute; DBP=diastolic blood pressure; LCM=lacosamide; Max=maximum; Min=minimum; mmHg=millimeters of mercury; MP=Maintenance Phase; SD=standard deviation; SBP=systolic blood pressure; TP=Titration Phase

a Baseline was the last non-missing value prior to or at randomization 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.

Data source: ISS Table EP.9.1.1

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Appendix 17. Vital sign changes with LCM intravenous infusion

Table 17.a Changes in Systolic BP in study SP616 (single dose)

Parameter (unit) LCM infusion duration group	Time point*	Day 2 am			
		oral LCM/ iv PBO		iv LCM/ oral PBO	
		n	mean (SD)	n	mean (SD)
SBP (mmHg)					
60min	Predose	10	-3.1 (6.77)	19	-0.6 (7.10)
	15min	10	0.6 (9.19)	19	-1.9 (6.37)
	30min	10	1.4 (15.49)	19	0.6 (8.47)
	45min	10	2.6 (12.58)	19	-1.1 (7.82)
	60min	10	3.5 (11.29)	19	0.2 (8.02)
	120min	10	2.6 (14.15)	19	4.5 (10.01)
30min	Predose	11	-0.2 (7.21)	19	-0.7 (13.50)
	10min	11	1.9 (9.46)	18	-1.5 (11.16)
	20min	11	2.2 (7.70)	19	-1.8 (9.69)
	30min	11	2.2 (9.58)	19	-0.7 (12.78)
	60min	11	0.3 (11.49)	19	0.4 (12.93)
	120min	11	2.4 (7.03)	19	1.2 (12.27)

Table 17.b Changes in diastolic BP in study SP616 (single dose)

Parameter (unit) LCM infusion duration group	Time point*	Day 2 am			
		oral LCM/ iv PBO		iv LCM/ oral PBO	
		n	mean (SD)	n	mean (SD)
DBP (mmHg)					
60min	Predose	10	-1.8 (10.36)	19	1.1 (7.18)
	10min	10	-0.8 (9.09)	19	1.1 (7.00)
	20min	10	2.9 (11.82)	19	2.4 (7.49)
	30min	10	1.0 (9.94)	19	0.0 (6.66)
	60min	10	2.2 (9.07)	19	1.6 (5.99)
	120min	10	1.4 (11.67)	19	3.6 (8.17)
30min	Predose	11	1.1 (6.20)	19	0.8 (9.68)
	15min	11	1.3 (4.82)	18	-0.3 (8.48)
	30min	11	1.7 (6.83)	19	-1.3 (8.35)
	45min	11	1.3 (6.92)	19	-0.5 (9.38)
	60min	11	2.5 (6.92)	19	1.6 (10.25)
	120min	11	3.1 (7.98)	19	1.0 (8.41)

Measured in the morning. SS= Safety set

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Appendix 17c. Summary of changes from Baseline1 in vital sign parameters by infusion duration and time point based on correct infusion duration/dose (SP757 SS)

Parameter (unit) LCM infusion duration group	Time point[a]	Day 1		Day 2	
		Dose 1 (am)	Dose 2 (pm)	Dose 3 (am)	Dose 4 (pm)
		Mean (SD)	mean (SD)	mean (SD)	mean (SD)
SBP (mmHg)					
30min (n=36)	Predose[b]	117.5 (11.79)	0.6 (11.16)	-2.6 (8.52)	0.1 (11.45)
	15min	0.5 (6.20)	2.8 (11.06)	-2.7 (10.06)	-0.5 (10.83)
	30min	0.6 (7.53)	2.6 (11.46)	-1.0 (10.16)	1.1 (10.25)
	120min	-0.6 (10.35)	1.9 (9.38)	0.5 (9.84)	3.5 (11.05)
15min (n=91)[c]	Predose[b]	120.4 (14.26)	4.2 (13.37)	-1.7 (12.07)	1.3 (13.62)
	7.5min	-0.9 (10.68)	3.4 (11.28)	-3.1 (12.97)	1.2 (12.41)
	15min	0.9 (10.06)	3.1 (11.32)	-1.9 (12.70)	1.8 (13.31)
	120min	1.3 (11.16)	3.4 (10.39)	-1.1 (12.31)	1.5 (14.01)
10min (n=20)[c]	Predose[b]	114.4 (9.07)	4.4 (11.01)	5.2 (12.17)	7.0 (8.68)
	5min	1.4 (7.67)	5.8 (8.51)	3.3 (12.88)	8.6 (10.99)
	10min	0.1 (5.34)	5.0 (9.82)	1.8 (11.71)	8.9 (9.38)
	120min	3.8 (11.20)	10.5 (9.78)	8.0 (10.43)	5.9 (13.08)

Parameter (unit) LCM infusion duration group	Time point[a]	Day 1		Day 2	
		Dose 1 (am)	Dose 2 (pm)	Dose 3 (am)	Dose 4 (pm)
		Mean (SD)	mean (SD)	mean (SD)	mean (SD)
DBP (mmHg)					
30min (n=36)	Predose[b]	73.5 (8.76)	0.8 (6.38)	-2.3 (6.40)	-2.8 (8.35)
	15min	-0.3 (7.91)	0.9 (7.25)	-2.2 (8.74)	-3.3 (7.46)
	30min	-0.1 (7.42)	0.5 (7.60)	-0.8 (7.48)	-2.0 (7.00)
	120min	-2.5 (8.27)	0.2 (6.92)	-2.2 (6.62)	-0.7 (7.64)
15min (n=91)[c]	Predose[b]	75.6 (10.69)	0.5 (8.61)	-0.9 (8.32)	-0.1 (8.45)
	7.5min	0.3 (7.57)	0.8 (8.99)	-1.2 (8.22)	0.4 (9.33)
	15min	1.2 (7.83)	1.5 (9.68)	0.3 (9.21)	0.0 (9.49)
	120min	1.1 (7.89)	1.7 (8.16)	-0.7 (8.97)	-0.5 (9.86)
10min (n=20)[c]	Predose[b]	72.1 (7.20)	1.8 (9.66)	2.4 (8.27)	1.0 (9.32)
	5min	-0.1 (5.67)	2.9 (9.78)	2.6 (10.73)	3.6 (9.84)
	10min	-0.6 (6.81)	2.0 (8.61)	2.1 (10.77)	1.2 (10.67)
	120min	1.0 (10.92)	4.8 (7.75)	2.2 (9.21)	3.3 (11.15)

Source: Pg. 668 and 669 of ISS.

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Appendix 18. Mean changes in weight by randomization group in EP S1

	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)
Body weight								
Baseline	364	76.5		75.1		78.8		78.5
Change end Titration	339	76.8		75.1		79.0		80.6
Change end of Maint	322	77.4		74.7		80.1		82.3
Change end of taper	33	73.2		72.9		74.6		69.8

Source: Sponsor's Table 9.5.1 ISS, original submission.

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Appendix 19. Specific ECG monitoring in the LCM database

8 ECG monitoring in Phase 2/3 studies in epilepsy EP S1

In the double-blind, placebo-controlled trials (SP667, 754 and 755) a standard 12-lead ECG was done at each visit (except Visit 2); plasma samples were performed as close as possible to the time of the ECG. At Visit 1 (Screening), one 12-lead ECG was done at any time to determine trial eligibility. At Visit 3 (Baseline) in SP667, three 12-lead ECGs were performed approximately 15 minutes apart prior to dosing; an additional ECG was performed 2-4 hours after dosing of trial medication at the approximate time of maximum plasma concentration (C_{max}). *The sponsor's OCP summary says Tmax is 0.5-4 hours so some of these assessments may have missed the Cmax.* At all other visits in SP667, one 12-lead ECG was performed 2-4 hours after dosing of trial medication. At Visit 3 (Baseline) in SP754 and SP755, three 12-lead ECGs were performed approximately 15 minutes apart prior to dosing. At all other visits in SP754 and SP755, 1 ECG was performed at any time after dosing.

During the double-blind phase of these studies, each ECG was transmitted to the central ECG facility for manual over-read by a cardiologist. All manual over-reads were done by a single cardiologist. The investigator assessed clinical relevance of each abnormal ECG. During the trial, if clinically relevant ECG abnormalities were detected, or **if a QTc interval ≥500ms and/or a QTc interval increase of ≥60ms** from the mean predose QTc value at Baseline was detected, a repeat ECG was performed 1 hour later.

ECG monitoring in the epilepsy open-label extension trials

In SP615, SP756, and SP774 ECGs were conducted at all clinic visits and read by central readers.

- ECG monitoring in IV studies

- In the single-dose Phase 1 trials for IV LCM (SP643, SP645, SP658, and SP834 standard 12-lead ECGs were taken at regular intervals. There was no central reading.

- In the Phase 2/3 trials of IV LCM (SP616 and SP757), 12-lead ECGs were conducted at several time points. In SP616, ECGs were performed during the Screening, Treatment, and End of Trial Phase. A single assessment was performed during the Screening Phase within 1 hour before the start of the IV placebo infusion. During the Treatment Phase (Days 1 and 2), an ECG was performed within 1 hour prior to trial medication in the morning. Several ECGs were conducted after the start of infusion of trial medication in the morning and evening. In SP757, an ECG was performed after the morning and evening infusion: within 1 hour prior to trial medication administration, approximately half-way through infusion, at the end of the infusion, and 2 hours after the start of infusion of trial medication. There was ECG central reading.

- ECG monitoring in healthy volunteers

A Phase 1 thorough QT/QTc interval trial, SP640, was designed specifically to assess the ECG Effects of LCM. ECG interval and morphology changes (based on 12-lead ECGs taken at specified time points) were analyzed based on ICH Guidance E14. For safety purposes, additional 12-lead ECGs were taken as specified in the protocol. There was central reading.

- ECG monitoring with the capsule formulation

Standard 12-lead ECGs were conducted on subjects in the supporting Phase 2 trials, SP586, SP598, and SP607.

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Appendix 20. Listing of patients with post baseline QTc (B) ≥ 450 ms (male) or ≥470 ms (female)

USUBJID	TRTGRP	VISIT	QTc(B) on treatment	QTc(B) baseline mean	QTc (B) change
Female					
755114201	Placebo	VISIT 4	471	436	35
667010205	LCM 200	VISIT 12	474	439	35
667014501	LCM 200	VISIT 6	475	440	35
667014501	LCM 200	VISIT 9	470	440	30
755106201	LCM 200	TRANSITION	472	424	48
667010206	LCM 400	VISIT 3	484	455	29
667010609	LCM 400	VISIT 6	471	443	28
754012904	LCM 400	VISIT 6	474	459	14
667015705	LCM 600	VISIT 3	487	438	49
Male					
667012805	Placebo	VISIT 6	453	420	33
667017701	Placebo	VISIT 8	451	390	61
755104305	Placebo	VISIT 4	454	397	56
667013204	LCM 200	VISIT 4	455	405	50
755114408	LCM 200	VISIT 5	451	413	38
667010617	LCM 400	TRANSITION	451	413	38
667012505	LCM 400	TRANSITION	455	418	37
667015602	LCM 400	VISIT 7	450	413	37
667016917	LCM 400	TRANSITION	451	434	17
667016924	LCM 400	TAPER	452	439	13
667016924	LCM 400	TAPER	454	439	15
667016924	LCM 400	VISIT 4	469	439	30
667016934	LCM 400	VISIT 10	450	427	23
667018807	LCM 400	VISIT 1	465	416	49
754011209	LCM 400	TRANSITION	450	408	42
754011807	LCM 400	VISIT 4	451	405	46
754011904	LCM 400	VISIT 7	451	441	10
754012413	LCM 400	TRANSITION	451	436	15
754012413	LCM 400	VISIT 8	451	436	15
754012702	LCM 400	TRANSITION	452	425	27
754015102	LCM 400	VISIT 6	472	423	50
754016006	LCM 400	VISIT 4	463	420	44
667010601	LCM 600	VISIT 7	457	431	26
667010612	LCM 600	VISIT 7	451	429	22

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Appendix 21. ECG outlier analyses in studies with LCM intravenous formulation

- IV Phase 1, single dose studies

The sponsor did not do a PR interval outlier analysis for the Phase 1 IV trials (SP643, SP645, SP658, and SP834). Overall, there were few subjects who met the QRS duration outlier criteria. The incidence of QRS duration outliers was similar for IV and oral administration and also similar between LCM 30-minute and 60-minute infusion durations. Only 1 subject had a QRS duration >120ms and none had a QRS duration >140ms. Across the Phase 1 IV trials in healthy volunteers, there was no clear evidence for QTc prolongation. In total, 85 healthy subjects across the 4 Phase 1 IV trials received IV LCM. Most subjects received a single dose of IV LCM 200, except in SP834, in which subjects received a single dose of IV LCM 50, 100, 150, or 300, and 4 subjects received IV placebo. In SP643, SP645, and SP658, no subject had a QTcB interval ≥500ms following IV LCM. In SP645 and SP658, no subject had an increase in QTcB interval ≥60ms following iv LCM. In SP834, QTc outlier analysis was not performed.

In SP643, QTc increases from Baseline were always below 60ms and all QTc values were <460ms, except for Subject 10020 (randomization number 80011) who had an increase of QTc from Baseline of more than 60ms (68ms) at 4 hours after starting the infusion during Treatment A. Further ECG recordings showed changes from Baseline of less than 60ms. The subject was withdrawn from the trial according to the withdrawal criterion of an increase of QTc from Baseline by more than 60ms as defined in the trial protocol. This case has been discussed under section 7.3: "Other AE of interest" of this review.

- Outliers in IV in Phase 2/3 IV LCM trials in subjects with partial-onset seizures

- Study SP616. The frequency of outliers in EP SP616 is presented in the following table.

Table 616a.Incidence of PR outliers during treatment phase in SP616.

	Cohort A (60min)		Cohort B (30min)	
	Oral Lacosamide/ IV Placebo	IV Lacosamide/ Oral Placebo	Oral Lacosamide/ IV Placebo	IV Lacosamide/ Oral Placebo
Parameter Criteria	n/ N (%)	n/ N (%)	n/ N (%)	n/ N (%)
Overall				
>200ms	2/ 10 (20.0)	3/ 20 (15.0)	3/ 11 (27.3)	2/ 19 (10.5)
>220ms	1/ 10 (10.0)	1/ 20 (5.0)	0/ 11	0/ 19
>250ms	0/ 10	0/ 20	0/ 11	0/ 19
Treatment-emergent/Baseline1				
>200ms	1/ 9 (11.1)	2/ 19 (10.5)	2/ 10 (20.0)	2/ 19 (10.5)
>220ms	1/ 10 (10.0)	1/ 20 (5.0)	0/ 11	0/ 19
>250ms	0/ 10	0/ 20	0/ 11	0/ 19
Treatment-emergent/Baseline2				
>200ms	2/ 10 (20.0)	2/ 19 (10.5)	3/ 11 (27.3)	2/ 18 (11.1)
>220ms	1/ 10 (10.0)	1/ 20 (5.0)	0/ 11	0/ 18
>250ms	0/ 10	0/ 20	0/ 11	0/ 18

Overall= subjects meeting the specified criteria at any timepoint during the Treatment Phase without regard to Baseline1 or Baseline2. n = Number of subjects meeting the specified criteria out of the set of subjects at risk (N). N = Number of subjects in the Safety Set for Overall and the number of subjects who did not meet the criteria at the specified Baseline for treatment-emergent summaries. Treatment-emergent is defined as meeting the criteria for any ECG during the Treatment Phase and not meeting the same criteria at the specified Baseline. Source: Sponsor's Appendix EP.11.3.2.

Overall, 15 to 27% of subjects met the PR interval outlier criteria. The frequency of outliers did not markedly differ between the oral and IV treatment groups, although there is a trend to more outliers in the oral LCM groups.

QRS interval outliers with >100 ms duration are presented in the following table.

Table 616b.. Incidence of TE QRS duration outliers with respect to baseline 1 at any time in SP616

	Cohort A (60min)		Cohort B (30min)	
	Oral Lacosamide/ IV Placebo	IV Lacosamide/ Oral Placebo	Oral Lacosamide/ IV Placebo	IV Lacosamide/ Oral Placebo
Parameter Criteria	n/ N (%)	n/ N (%)	n/ N (%)	n/ N (%)
Overall				
>100ms	4/ 10 (40.0)	8/ 20 (40.0)	3/ 11 (27.3)	6/ 19 (31.6)
>120ms	1/ 10 (10.0)	1/ 20 (5.0)	0/ 11	0/ 19
>140ms	0/ 10	0/ 20	0/ 11	0/ 19
Treatment-emergent/Baseline1				
>100ms	1/ 7 (14.3)	4/ 16 (25.0)	2/ 10 (20.0)	4/ 17 (23.5)
>120ms	0/ 9	1/ 20 (5.0)	0/ 11	0/ 19
>140ms	0/ 10	0/ 20	0/ 11	0/ 19
Treatment-emergent/Baseline2				
>100ms	1/ 7 (14.3)	4/ 16 (25.0)	2/ 10 (20.0)	6/ 18 (33.3)
>120ms	1/ 10 (10.0)	1/ 20 (5.0)	0/ 11	0/ 18
>140ms	0/ 10	0/ 20	0/ 11	0/ 18

Overall is the number of subjects meeting the specified criteria at any timepoint during the Treatment Phase without regard to Baseline1 or Baseline2. n = Number of subjects meeting the specified criteria out of the set of subjects at risk (N). N = Number of subjects in the Safety Set for Overall and the number of subjects who did not meet the criteria at the specified Baseline for treatment-emergent summaries. Treatment-emergent is defined as meeting the criteria for any ECG during the Treatment Phase and not meeting the same criteria at the specified Baseline. Source: Appendix EP 11.3.8.

Overall, 14 to 25% fulfill the QRS duration outlier criteria. The incidence of QRS duration outliers was similar for IV and oral administration and also similar between LCM 30-minute and 60-minute infusion durations. No subject had a QTc interval ≥500ms. In addition, no subject had a change from Baseline 1 (predose in SP616) ≥60ms.

> *In SP616, a total of 60 subjects were treated with IV LCM, with 10 to 20 patients per treatment group. 15-30 % of patients had outlier results in PR and QRS intervals in both treatment groups. No definitive conclusions can be made about the comparative safety of the 30 and 60 ms IV infusion and or the oral versus IV formulation.*

- SP757

Across all infusion duration groups and dose categories in SP757 the frequency of PR interval outliers appear to occur more often in the 30-minute infusion as compared to the other durations (15 and 10 minutes). Two subjects in the 15-minute infusion group had a treatment-emergent PR interval >250ms while on LCM 200mg/day. The number is too small to draw any conclusions regarding comparative safety of these infusion rates. The incidence of PR interval outliers with respect to Baseline1 (Baseline1=ECG prior to first IV LCM administration) anytime during the Treatment Phase by dose category is presented in the following table.

Table. 757a. PR interval outliers in SP757

Incidence of treatment-emergent PR interval outliers with respect to Baseline1 anytime during the Treatment Phase by dose category (LCM 200mg/day-400mg/day, LCM 500mg/day-600mg/day, LCM 700mg/day-800mg/day) (SP757 SS)

	LCM infusion duration		
	30-minute	15-minute	10-minute
Dose category / PR criteria	n/N (%)	n/N (%)	n/N (%)
LCM 200-400mg/day			
>200ms	6/20 (30)	11/58 (19)	0/10
>220ms	3/21 (14)	5/63 (8)	2/13 (15)
>250ms	0/21	2/63 (3)	0/13
LCM 500-600mg/day			
>200ms	3/18 (17)	1/29 (3)	1/6 (17)
>220ms	2/18 (11)	1/30 (3)	1/7 (14)
>250ms	0/19	0/30	0/7
LCM 700-800mg/day			
>200ms	-	2/7 (29)	-
>220ms	-	0/7	-
>250ms	-	0/7	-

LCM=lacosamide; ms=millisecond; SS=Safety Set
Note: n=number of subjects meeting the specified criteria out of the set of subjects at risk (N); N=The number of subjects who did not meet the criteria at Baseline1.
Data source: 5.3.5.2.7 EP: SP757 Table 12.5.2

As seen in this table, approximately 24% of patients in the 30 minute infusion group, 15% in the 15 minutes infusion group and 4% of the 10-minute infusion group, fulfill the >200 PR outlier criterion as compared to baseline 1. A higher percentage of patients also had QRS >100 ms in the 15 and 10-min infusion as compared to the 30 min infusion.

Table 757b. Treatment emergent QRS outliers in SP757.

QRS criteria	LCM infusion duration		
	30-minute	15-minute	10-minute
	n/N (%)	n/N (%)	n/N (%)
>100ms	7/32 (22)	27/82 (33)	5/17 (29)
>120ms	0/40	2/99 (2)	0/20
>140ms	0/40	0/100	0/20

LCM=lacosamide; ms=millisecond; SS=Safety Set
Note: n=number of subjects meeting the specified criteria out of the set of subjects at risk (N); N=The number of subjects who did not meet the criteria at Baseline1.
Source: Sponsor's table in page 168 of Cardiac Report.

There were no subjects who had a QTcF interval ≥500ms during the trial. There were no subjects who had a change from Baseline2 ≥60ms (Baseline2=Baseline ECG from subject's original trial) in QTcF interval during the trial. One subject had a change from Baseline1 ≥60ms (Baseline1=ECG prior to first iv LCM administration) in both QTcF and QTcB intervals; this subject did not discontinue from the trial. Also in SP757, 1 subject had a QTcB interval ≥500ms post-Baseline during the trial; this subject was discontinued from the trial because of this increase in QTcB. There were 2 subjects who had a change from Baseline1 ≥60ms in QTcB interval during the trial and there were 4 subjects who had a change from Baseline2 ≥60ms in QTcB interval during the trial. These subjects (change from Baseline1 or Baseline2 ≥60ms) were not discontinued from the trial.

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Appendix 22. Cases of Euphoric mood in EPILEPSY population

USUBJID	TRTGRP	AEterm	AEDROP	RELATED	OUTCOME	LLTDM	CRELSTDY	PART	LCM dose
667018805	LCM 600mg	Elation of mood	no	yes	recovering/ resolving	ELEVATED MOOD	424	OLE	600
754017102	LCM 400mg	Feeling "high"	no	yes	resolved	FEELING HIGH	22	DB	400
		Feeling high	yes	yes	resolved	FEELING HIGH	27	DB	400
754017405	LCM 600mg	Mild euphoria	no	yes	resolved	EUPHORIA	122	DB	400

Source: AE datasets submitted with SUR.

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Appendix 23.a. Concomitant diagnosis at baseline 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 (%)
Blood and lymphatic system disorders	7 (1.9)	5 (1.9)	15 (3.2)	6 (3.0)
Cardiac disorders	17 (4.7)	3 (1.1)	15 (3.2)	5 (2.5)
Congenital, familial and genetic disorders	15 (4.1)	14 (5.2)	32 (6.8)	21 (10.3)
Ear and labyrinth disorders	17 (4.7)	4 (1.5)	29 (6.2)	12 (5.9)
Endocrine disorders	17 (4.7)	17 (6.3)	27 (5.7)	11 (5.4)
Eye disorders	49 (13.5)	37 (13.7)	75 (15.9)	29 (14.3)
Gastrointestinal disorders	48 (13.2)	33 (12.2)	83 (17.6)	37 (18.2)
General disorders and administration site conditions	26 (7.1)	15 (5.6)	50 (10.6)	28 (13.8)
Hepatobiliary disorders	3 (0.8)	4 (1.5)	2 (0.4)	0
Immune system disorders	52 (14.3)	30 (11.1)	86 (18.3)	35 (17.2)
Infections and infestations	22 (6.0)	17 (6.3)	35 (7.4)	17 (8.4)
Injury, poisoning and procedural complications	13 (3.6)	5 (1.9)	20 (4.2)	6 (3.0)
Investigations	17 (4.7)	6 (2.2)	39 (8.3)	7 (3.4)
Metabolism and nutrition disorders	43 (11.8)	24 (8.9)	66 (14.0)	26 (12.8)
Musculoskeletal and connective tissue disorders	67 (18.4)	47 (17.4)	110 (23.4)	47 (23.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.5)	8 (3.0)	11 (2.3)	2 (1.0)
Nervous system disorders	152 (41.8)	89 (33.0)	226 (48.0)	106 (52.2)
Psychiatric disorders	83 (22.8)	44 (16.3)	110 (23.4)	59 (29.1)

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Renal and urinary disorders	14 (3.8)	8 (3.0)	13 (2.8)	6 (3.0)
Reproductive system and breast disorders	29 (8.0)	7 (2.6)	43 (9.1)	18 (8.9)
Respiratory, thoracic and mediastinal disorders	29 (8.0)	9 (3.3)	55 (11.7)	26 (12.8)
Skin and subcutaneous tissue disorders	30 (8.2)	22 (8.1)	52 (11.0)	28 (13.8)
Social circumstances	5 (1.4)	9 (3.3)	10 (2.1)	8 (3.9)
Surgical and medical procedures	5 (1.4)	0	7 (1.5)	1 (0.5)
Vascular disorders	32 (8.8)	15 (5.6)	58 (12.3)	21 (10.3)

Appendix 23.b. Concomitant medications at baseline in SOCs with incidence of >0.5% in any treatment group

		Lacosamide		
Level 2 ATC Class/ Level 4 ATC Class	Placebo (N=364) n (%)	200mg/day (N=270) n (%)	400mg/day (N=471) n (%)	600mg/day (N=203) n (%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM, C09	13 (3.6)	10 (3.7)	27 (5.7)	11 (5.4)
ANALGESICS, N02	65 (17.9)	57 (21.1)	106 (22.5)	57 (28.1)
ANTIANEMIC PREPARATIONS, B03	17 (4.7)	15 (5.6)	39 (8.3)	16 (7.9)
ANTIBACTERIALS FOR SYSTEMIC USE, J01	25 (6.9)	16 (5.9)	30 (6.4)	20 (9.9)
ANTIBIOTICS AND CHEMOTHER. FOR DERMATOLOGICAL USE, D06	2 (0.5)	0	3 (0.6)	2 (1.0)
ANTIDIARR.,INTEST. ANTIINFL./ANTIINFECT. AGENTS, A07	7 (1.9)	6 (2.2)	12 (2.5)	5 (2.5)
ANTIFUNGALS FOR DERMATOLOGICAL USE, D01	2 (0.5)	3 (1.1)	3 (0.6)	2 (1.0)
ANTIHYPERTENSIVES, C02	2 (0.5)	0	0	2 (1.0)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, M01	50 (13.7)	33 (12.2)	83 (17.6)	48 (23.6)

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ANTITHROMBOTIC AGENTS, B01	13 (3.6)	4 (1.5)	17 (3.6)	8 (3.9)
BETA BLOCKING AGENTS, C07	19 (5.2)	6 (2.2)	19 (4.0)	8 (3.9)
BILE AND LIVER THERAPY, A05	0	4 (1.5)	0	0
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS, B05	1 (0.3)	2 (0.7)	3 (0.6)	1 (0.5)
CALCIUM CHANNEL BLOCKERS, C08	6 (1.6)	1 (0.4)	9 (1.9)	3 (1.5)
CARDIAC THERAPY, C01	4 (1.1)	0	6 (1.3)	1 (0.5)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS, D07	2 (0.5)	2 (0.7)	7 (1.5)	3 (1.5)
COUGH AND COLD PREPARATIONS, R05	10 (2.7)	14 (5.2)	22 (4.7)	10 (4.9)
DIURETICS, C03	6 (1.6)	5 (1.9)	13 (2.8)	10 (4.9)
DRUGS FOR ACID RELATED DISORDERS, A02	25 (6.9)	12 (4.4)	37 (7.9)	24 (11.8)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS, A03	5 (1.4)	2 (0.7)	8 (1.7)	1 (0.5)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, R03	15 (4.1)	4 (1.5)	11 (2.3)	9 (4.4)
DRUGS FOR TREATMENT OF BONE DISEASES, M05	3 (0.8)	4 (1.5)	9 (1.9)	8 (3.9)
DRUGS USED IN DIABETES, A10	9 (2.5)	2 (0.7)	6 (1.3)	2 (1.0)
IMMUNOSUPPRESSIVE AGENTS, L04	0	0	3 (0.6)	0
LAXATIVES, A06	5 (1.4)	4 (1.5)	14 (3.0)	5 (2.5)
MINERAL SUPPLEMENTS, A12	17 (4.7)	15 (5.6)	41 (8.7)	18 (8.9)
MUSCLE RELAXANTS, M03	0	1 (0.4)	4 (0.8)	2 (1.0)
NASAL PREPARATIONS, R01	15 (4.1)	7 (2.6)	21 (4.5)	12 (5.9)
OPHTHALMOLOGICALS, S01	6 (1.6)	7 (2.6)	9 (1.9)	4 (2.0)
PSYCHOANALEPTICS, N06	50 (13.7)	23 (8.5)	66 (14.0)	40 (19.7)
PSYCHOLEPTICS, N05	17 (4.7)	9 (3.3)	21 (4.5)	9 (4.4)

b(4)

SERUM LIPID REDUCING AGENTS, C10	24 (6.6)	7 (2.6)	29 (6.2)	18 (8.9)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM, G03	28 (7.7)	17 (6.3)	32 (6.8)	13 (6.4)
THYROID THERAPY, H03	13 (3.6)	11 (4.1)	29 (6.2)	11 (5.4)
UROLOGICALS, G04	4 (1.1)	3 (1.1)	5 (1.1)	3 (1.5)
VACCINES, J07	3 (0.8)	4 (1.5)	3 (0.6)	1 (0.5)
VASOPROTECTIVES, C05	5 (1.4)	2 (0.7)	4 (0.8)	0
VITAMINS, A11	42 (11.5)	25 (9.3)	97 (20.6)	40 (19.7)

b(4)

Appendix 24. Analysis of weight in EP S1

Discontinuation due to AE by Dose and BMI

The following table shows Discontinuation due to AE by Dose and BMI in the E1Pool (studies 667, 754, and 755).

	Dose																All
	0				200				400				600				
	Disc AE				Disc AE				Disc AE				Disc AE				
	Yes		No		Yes		No		Yes		No		Yes		No		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
BMI <18.5	1	5.9	16	94.1	1	11.1	8	88.9	3	18.8	13	81.3	3	42.9	4	57.1	49
18.5-24	7	5.1	130	94.9	14	11.3	110	88.7	37	21.5	135	78.5	26	36.1	46	63.9	505
25-29.9	6	4.8	118	95.2	5	6.2	76	93.8	20	14.0	123	86.0	18	26.5	50	73.5	416
>=30	4	4.9	78	95.1	5	9.6	47	90.4	20	14.7	116	85.3	11	20.0	44	80.0	325
All	18	5.0	342	95.0	25	9.4	241	90.6	80	17.1	387	82.9	58	28.7	144	71.3	1295

Source: FDA statistician, Tristan Massie, Ph.D.

Discontinuations due to AE increased with increasing dose ($p<0.0001$) and there was some evidence that they increased with decreasing BMI ($p=0.04$).For the 600 mg group the time to dropout due to adverse event decreased with BMI category (increasing BMI). A test for difference between the "survival" curves yields a p-value of 0.08.

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