**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]<br><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;<br>≥10.0xULN |
| ALT (U/L) | NA | ≥3.0xULN; ≥5.0xULN;<br>≥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 |

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**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<br>Treatment | Parameter:<br>Markedly Abnormal Value | Site Number / Subject Number |
|---|---|---|
| A (60min)<br>IV Lacosamide/ Oral Placebo | WBC: <=3.0 G/l | 106/10526## |
| | Neutrophils Abs: <1.5 G/l | 106/10526## |
| B (30min)<br>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 | 268/11487*, 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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