



Clinical trial results:

An Open-Label Study to Determine Safety, Tolerability, and Efficacy of Long-Term Oral Lacosamide as Adjunctive Therapy in Children With Epilepsy

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2011-001559-35 |
| Trial protocol | BE DE HU IT Outside EU/EEA PL FR |
| Global end of trial date | 18 May 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2021 |
| First version publication date | 03 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | SP848 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00938912 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB BIOSCIENCES, Inc. |
| Sponsor organisation address | 8010 Arco Corporate Drive, Raleigh, United States, NC 27617 |
| Public contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |
| Scientific contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |

Notes:

Paediatric regulatory details

| | |
|--|----------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000402-PIP03-17 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 July 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 May 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 May 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To obtain information about the safety, tolerability, and pharmacokinetics (PK) of lacosamide (LCM) during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long term exposure

Protection of trial subjects:

All participants were closely monitored during the conduct of the study. Microvettes to minimize blood volume in lab draws and topical analgesics were encouraged for needle sticks. Permitted opportunistic blood draws (piggyback study blood collection on health required blood draws).

Background therapy:

Background therapy with anti-seizure medication (ASM) as permitted in the protocol and vagus nerve stimulation (VNS) permitted.

Evidence for comparator:

Not applicable.

| | |
|---|------------------|
| Actual start date of recruitment | 09 December 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 10 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | China: 61 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Hungary: 44 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Japan: 46 |
| Country: Number of subjects enrolled | Mexico: 22 |
| Country: Number of subjects enrolled | Poland: 22 |
| Country: Number of subjects enrolled | Ukraine: 42 |
| Country: Number of subjects enrolled | United States: 112 |
| Worldwide total number of subjects | 365 |
| EEA total number of subjects | 82 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 21 |
| Children (2-11 years) | 229 |
| Adolescents (12-17 years) | 114 |
| Adults (18-64 years) | 1 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study started to enroll study participants in December 2009 and concluded in May 2021. Eligible study participants were allowed to roll over from study SP0847 (NCT00938431), SP0966 (NCT01969851) and EP0060 (NCT02710890) and eligible study participants were also allowed to directly enroll into the study.

Pre-assignment

Screening details:

Total 366 participants were enrolled. Among 366, 365 participants received treatment. One participant was enrolled, but did not receive treatment prior to discontinuing due to ineligibility.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-------------------------------|
| Arm title | Lacosamide (All Participants) |
|------------------|-------------------------------|

Arm description:

Participants aged greater than or equal to (≥ 1) month received either lacosamide (LCM) 2-12 milligrams/kilograms/day (mg/kg/day) (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lacosamide |
| Investigational medicinal product code | |
| Other name | LCM |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants aged ≥ 1 month received either LCM 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 600 mg/day based on body weight, whichever was lower) for approximately 2 years at prespecified time points.

| | |
|--|---------------|
| Investigational medicinal product name | Lacosamide |
| Investigational medicinal product code | |
| Other name | LCM |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Participants aged ≥ 1 month received either LCM 2-12 mg/kg/day (oral solution) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day based on body weight, whichever was lower) for approximately 2 years at prespecified time points.

| Number of subjects in period 1 | Lacosamide (All Participants) |
|--|--------------------------------------|
| Started | 365 |
| Completed | 254 |
| Not completed | 111 |
| Participant was scheduled for lobal resection | 1 |
| No longer wished to participate in the study | 1 |
| Protocol Deviation | 2 |
| Participant had a creatinine clearance <30 mL/min | 1 |
| Participant self adjusted antiepileptic medication | 1 |
| Consent withdrawn by subject | 28 |
| Participant moved to another city | 1 |
| Adverse event, non-fatal | 24 |
| Adverse event, fatal | 1 |
| Did not meet Eligibility criteria | 1 |
| Participant relocated not related to AE | 1 |
| Participant experienced break through seizures | 1 |
| Lost to follow-up | 4 |
| Lack of efficacy | 43 |
| Participant needed prohibit medication | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Lacosamide (All Participants) |
|-----------------------|-------------------------------|

Reporting group description:

Participants aged greater than or equal to (≥ 1) month received either lacosamide (LCM) 2-12 milligrams/kilograms/day (mg/kg/day) (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years.

| Reporting group values | Lacosamide (All Participants) | Total | |
|--|-------------------------------|-------|--|
| Number of subjects | 365 | 365 | |
| Age Categorical Units: participants | | | |
| ≤ 18 years | 365 | 365 | |
| Between 18 and 65 years | 0 | 0 | |
| ≥ 65 years | 0 | 0 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 9.28 | | |
| standard deviation | ± 4.55 | - | |
| Sex: Female, Male Units: participants | | | |
| Female | 173 | 173 | |
| Male | 192 | 192 | |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Lacosamide (All Participants) |
| Reporting group description: Participants aged greater than or equal to (≥ 1) month received either lacosamide (LCM) 2-12 milligrams/kilograms/day (mg/kg/day) (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years. | |
| Subject analysis set title | Lacosamide (All Participants) (SS) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants aged ≥ 1 month received either LCM 2-12 mg/kg/day (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years. Participants formed the Safety Set (SS) which included all enrolled study participants who took at least 1 dose of LCM in this study. | |
| Subject analysis set title | Lacosamide (All Participants) (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants aged ≥ 1 month received either LCM 2-12 mg/kg/day (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years. Participants formed the Full Analysis Set (FAS) which included all study participants in the SS who had at least 1 completed post-Baseline seizure diary. | |

Primary: Number of Participants With At least One Treatment-Emergent Adverse Event (TEAE)

| | |
|--|---|
| End point title | Number of Participants With At least One Treatment-Emergent Adverse Event (TEAE) ^[1] |
| End point description: An AE is any untoward medical occurrence in a participant or clinical investigation study participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. TEAEs were defined as those events which started on or after the date of first SP848 LCM administration and occurred within 30 days after last dose of LCM, or whose severity worsened on or after the date of first SP848 LCM administration. The Safety Set (SS) consisted of all enrolled study participants who took at least 1 dose of LCM in this study. | |
| End point type | Primary |
| End point timeframe: From Baseline to End of Safety Follow-Up (up to 4.3 years) | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized in tables as descriptive statistics only.

| End point values | Lacosamide (All Participants) (SS) | | | |
|-----------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 365 | | | |
| Units: participants | 336 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Number of Participants With Serious Adverse Events (SAEs) ^[2] |
|-----------------|--|

End point description:

SAE was any untoward medical occurrence that at any dose resulted in death, is life-threatening, required in participant hospitalization or prolongation of existing hospitalization, is a congenital anomaly or birth defect, is an infection that requires treatment with parenteral antibiotics, other important medical events which based on medical or scientific judgement may jeopardize the participants, or may require medical or surgical intervention to prevent any of the above. The SS consisted of all enrolled study participants who took at least 1 dose of LCM in this study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to End of Safety Follow-Up (up to 4.3 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized in tables as descriptive statistics only.

| End point values | Lacosamide (All Participants) (SS) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 365 | | | |
| Units: participants | 82 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants that withdraw due to a Treatment-Emergent Adverse Event

| | |
|-----------------|---|
| End point title | Number of participants that withdraw due to a Treatment-Emergent Adverse Event ^[3] |
|-----------------|---|

End point description:

TEAEs were defined as those events which started on or after the date of first SP848 LCM administration and occurred within 30 days after last dose of LCM, or whose severity worsened on or after the date of first SP848 LCM administration. The SS consisted of all enrolled study participants who took at least 1 dose of LCM in this study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to End of Safety Follow-Up (up to 4.3 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this endpoint. Results were summarized in tables as descriptive statistics only.

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Lacosamide (All Participants) (SS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 365 | | | |
| Units: participants | 27 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants With $\geq 50\%$ reduction in 28-day partial-onset seizure frequency

| | |
|-----------------|---|
| End point title | Percentage of participants With $\geq 50\%$ reduction in 28-day partial-onset seizure frequency |
|-----------------|---|

End point description:

A 50% responder is a participant experiencing a $\geq 50\%$ reduction in partial-onset seizure frequency per 28 days from Baseline to end of specified time interval, else it is non-responder. For rollover participants, Baseline values from previous pediatric studies were designated as Baseline values in SP848. Baseline value for seizure counts for directly enrolled participants were taken from historical seizure count CRF/eCRF module in combination with seizure diary data collected from date of Screening Visit to day prior to date of first dose of LCM. Participants from EP0060 RxL enrollment group had no baseline data due to taking oral LCM prior to EP0060. FAS consisted of all participants in the SS who had at least 1 completed post-Baseline seizure diary. Number of participants analyzed included those participants who were evaluable for assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to End of Treatment Period (up to 4.2 years)

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Lacosamide (All Participants) (FAS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 308 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 53.6 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in 28 Day partial-onset seizure frequency to the end of the Treatment Period

| | |
|-----------------|---|
| End point title | Percent change from Baseline in 28 Day partial-onset seizure frequency to the end of the Treatment Period |
|-----------------|---|

End point description:

Percent change in seizure frequency per 28 days (PCH) from Baseline value (B) to Treatment Period

interval (T) was defined as: $PCH = [(SFT - SFB) / SFB] \times 100$ where, SFT denoted seizure frequency during Treatment Period for relative interval in open-label study and SFB denoted baseline seizure frequency. For both periods, frequency was standardized to number of seizures per 28 days. For rollover participants, Baseline value from previous studies were designated as Baseline values in SP848. Baseline value for seizure counts for directly enrolled participants were taken from historical seizure count case report form (CRF)/electronic CRF (CRF/eCRF) module in combination with seizure diary data collected from date of Screening Visit to day prior to date of first dose of LCM. Participants from EP0060 RxL enrollment group had no baseline data due to taking oral LCM prior to EP0060. Analysis set was FAS. Number of participants analyzed: participants who were evaluable for the assessment.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to End of Treatment Period (up to 4.2 years) | |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Lacosamide (All Participants) (FAS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 308 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -24.13 (\pm 112.08) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants With $\geq 75\%$ reduction in 28-day partial-onset seizure frequency

| | |
|-----------------|---|
| End point title | Percentage of participants With $\geq 75\%$ reduction in 28-day partial-onset seizure frequency |
|-----------------|---|

End point description:

A 75% responder is a participant experiencing a $\geq 75\%$ reduction in partial-onset seizure frequency per 28 days from Baseline to end of specified time interval, else it is non-responder. For rollover participants, Baseline values from previous pediatric studies were designated as Baseline values in SP848. Baseline value for seizure counts for directly enrolled participants were taken from historical seizure count CRF/eCRF module in combination with seizure diary data collected from date of Screening Visit to day prior to date of first dose of LCM. Participants from EP0060 RxL enrollment group had no baseline data due to taking oral LCM prior to EP0060. FAS consisted of all participants in the SS who had at least 1 completed post-Baseline seizure diary. Number of participants analyzed included those participants who were evaluable for assessment.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to End of Treatment Period (up to 4.2 years) | |

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Lacosamide (All Participants) (FAS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 308 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seizure days per 28 days for participants with generalized seizures

| | |
|-----------------|---|
| End point title | Number of seizure days per 28 days for participants with generalized seizures |
|-----------------|---|

End point description:

A seizure day was defined as a day where any type of seizure was reported in the seizure diary and seizures were assessed. Days in the seizure diary which were marked as "not done" on the CRF/eCRF were not counted as seizure-free days. The FAS consisted of all study participants in the SS who had at least 1 completed post-Baseline seizure diary. Here, number of participants analyzed included those participants who were evaluable for the assessment and number analyzed (n) included those participants who were evaluable at specified time points only.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 72, 84 and 96

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Lacosamide (All Participants) (FAS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 47 | | | |
| Units: seizure days per 28 days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=47) | 14.59 (± 11.94) | | | |
| Week 8 (n=46) | 14.83 (± 12.24) | | | |
| Week 12 (n=46) | 13.68 (± 12.62) | | | |
| Week 20 (n=46) | 12.57 (± 12.58) | | | |
| Week 28 (n=43) | 13.10 (± 12.63) | | | |
| Week 36 (n=43) | 11.43 (± 11.93) | | | |
| Week 44 (n=40) | 9.24 (± 11.23) | | | |
| Week 52 (n=41) | 10.48 (± 11.68) | | | |
| Week 60 (n=39) | 10.31 (± 11.84) | | | |

| | | | | |
|----------------|--------------------|--|--|--|
| Week 72 (n=39) | 11.15 (± 12.10) | | | |
| Week 84 (n=38) | 11.87 (± 12.45) | | | |
| Week 96 (n=37) | 10.73 (± 11.77) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved a seizure-free status

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved a seizure-free status |
|-----------------|---|

End point description:

Study participants were considered seizure-free for a given period if they completed the period, reported zero seizures during the period, and had no more than 10% of days in the period for which seizure data were not available (ie, "not done" was noted on the Seizure Frequency CRF/eCRF module). The FAS consisted of all study participants in the SS who had at least 1 completed post-Baseline seizure diary. Here, number of participants analyzed included those participants who were evaluable for the assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to End of Treatment Period (up to 4.2 years)

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Lacosamide (All Participants) (FAS) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 323 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 7.4 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to End of Safety Follow-Up (up to 4.3 years)

Adverse event reporting additional description:

TEAEs were defined as those events which started on or after the date of first SP848 LCM administration and occurred within 30 days after last dose of LCM, or whose severity worsened on or after the date of first SP848 LCM administration.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Lacosamide (All Participants) (SS) |
|-----------------------|------------------------------------|

Reporting group description:

Participants aged ≥ 1 month received either LCM 2-12 mg/kg/day (oral solution) or 100-600 mg/day (tablet) at a level to optimize tolerability and seizure control (maximum dose of 12 mg/kg/day or 600 mg/day based on body weight, whichever was lower) for approximately 2 years. Participants formed the SS which included all enrolled study participants who took at least 1 dose of LCM in this study.

| Serious adverse events | Lacosamide (All Participants) (SS) | | |
|---|------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 82 / 365 (22.47%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Astrocytoma, low grade | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 365 (1.10%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sleep apnoea syndrome | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Affective disorder | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination, auditory | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nightmare | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sleep disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Substance-induced psychotic disorder | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foreign body aspiration | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb traumatic amputation | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Skull fracture | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cyanosis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 21 / 365 (5.75%) | | |
| occurrences causally related to treatment / all | 4 / 29 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status epilepticus | | | |
| subjects affected / exposed | 11 / 365 (3.01%) | | |
| occurrences causally related to treatment / all | 2 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 5 / 365 (1.37%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 6 / 365 (1.64%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Seizure cluster | | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Partial seizures | | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalitis autoimmune | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Grand mal convulsion | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Altered state of consciousness | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clonic convulsion | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neurotoxicity | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lethargy | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor skills impaired | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Simple partial seizures | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Coagulopathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 8 / 365 (2.19%) | | |
| occurrences causally related to treatment / all | 3 / 19 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intussusception | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic tooth displacement | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|-----------------|--|--|
| disorders | | | |
| Atlantoaxial instability | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 365 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Urinary tract infection | | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillitis | | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchiolitis | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute tonsillitis | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erythema infectiosum | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia viral | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia mycoplasmal | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection fungal | | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperammonaemia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| | | | |
|---|------------------------------------|--|--|
| Non-serious adverse events | Lacosamide (All Participants) (SS) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 291 / 365 (79.73%) | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 25 / 365 (6.85%) | | |
| occurrences (all) | 55 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 45 / 365 (12.33%) | | |
| occurrences (all) | 97 | | |

| | | | |
|--|-------------------|--|--|
| Somnolence | | | |
| subjects affected / exposed | 74 / 365 (20.27%) | | |
| occurrences (all) | 100 | | |
| Dizziness | | | |
| subjects affected / exposed | 69 / 365 (18.90%) | | |
| occurrences (all) | 114 | | |
| Tremor | | | |
| subjects affected / exposed | 21 / 365 (5.75%) | | |
| occurrences (all) | 23 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 80 / 365 (21.92%) | | |
| occurrences (all) | 126 | | |
| Fatigue | | | |
| subjects affected / exposed | 21 / 365 (5.75%) | | |
| occurrences (all) | 31 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 77 / 365 (21.10%) | | |
| occurrences (all) | 149 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 40 / 365 (10.96%) | | |
| occurrences (all) | 52 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 21 / 365 (5.75%) | | |
| occurrences (all) | 32 | | |
| Nausea | | | |
| subjects affected / exposed | 25 / 365 (6.85%) | | |
| occurrences (all) | 35 | | |
| Constipation | | | |
| subjects affected / exposed | 25 / 365 (6.85%) | | |
| occurrences (all) | 34 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 19 / 365 (5.21%) | | |
| occurrences (all) | 29 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--------------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 36 / 365 (9.86%) 43 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 91 / 365 (24.93%) 253 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 86 / 365 (23.56%) 167 | | |
| Pharyngitis subjects affected / exposed occurrences (all) | 37 / 365 (10.14%) 48 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 29 / 365 (7.95%) 35 | | |
| Influenza subjects affected / exposed occurrences (all) | 29 / 365 (7.95%) 38 | | |
| Viral infection subjects affected / exposed occurrences (all) | 21 / 365 (5.75%) 36 | | |
| Bronchitis subjects affected / exposed occurrences (all) | 26 / 365 (7.12%) 40 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 20 / 365 (5.48%) 29 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 20 / 365 (5.48%) 24 | | |
| Ear infection subjects affected / exposed occurrences (all) | 19 / 365 (5.21%) 27 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|------------------------|--|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 26 / 365 (7.12%) 28 | | |
|--|------------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 November 2009 | The AEs of special interest were revised to reflect the sponsor's current understanding of the potential risks of LCM based on a comprehensive review of the data from clinical trials and commitments to regulatory agencies. The liver function test (LFT) withdrawal criteria were revised to reflect the sponsor's current understanding of the safety profile of LCM based on a comprehensive review of the data from clinical trials. |
| 13 December 2010 | <p>Based on the analysis of SP847 Cohort 1 (study participants aged 5 to 11 years) safety and PK data, the maximum permitted LCM dose in SP848 was 12mg/kg/day (for study participants weighing up to 50kg) or 600mg/day (for study participants weighing >50kg).</p> <p>The decision to re-insert additional withdrawal criteria and follow-up recommendations for abnormal LFTs was based on the following:</p> <ol style="list-style-type: none">1. Newly adopted FDA Guidance on Drug-Induced Liver Injury (July 2009) and a recommendation from the FDA to re-insert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols.2. Although no new liver-related safety issues with LCM had been identified, LFT abnormal had been added as a postmarketing adverse drug reaction in the LCM Company Core Data Sheet and the EU Summary of Product Characteristics. Therefore, LCM protocols were amended to reflect this addition. <p>With these revisions, liver-related safety signals continued to be detected via protocol-directed monitoring and additional follow up in ongoing and future LCM clinical studies.</p> <p>In addition, the protocol was revised to allow enrollment of study participants who had participated in other future LCM pediatric clinical studies in epilepsy (ie, in addition to SP847) to provide the opportunity to continue receiving LCM treatment in SP848.</p> |
| 29 July 2011 | <p>The sponsor's name was changed from SCHWARZ to UCB BIOSCIENCES, INC. Specific sponsor contact information was updated. As recommended by FDA, text was added or modified to make it clear that maximum permitted LCM dose in SP848 was 12mg/kg/day or 600mg/day, whichever was lower. As recommended by FDA, Columbia-Suicide Severity Rating Scale (C-SSRS) was added to evaluate and identify study participants at risk for suicide while participating in a clinical study of a drug with CNS activity. Oral solution formulation of LCM used in this study was revised to contain 10mg/mL of drug substance (formerly containing 15mg/mL of drug substance). UCB, in agreement with the Committee for Medicinal Products for Human Use, initiated the recall of VIMPAT syrup 15mg/mL due to a quality defect related to the formation of a flake-like precipitate of LCM in the syrup. UCB received approval for a 10mg/mL syrup; thus, all study participants in study were transitioned to LCM 10mg/mL. Also, UCB did not receive any reports from investigative sites of the appearance of these flake-like precipitants in the clinical trial supplies of LCM 15mg/mL syrup formulation used in SP848. All study participants were required to have a 12-lead ECG conducted at LCM maximum plasma concentration (C_{max}) 1 week after an initial LCM dose increase. This ECG could have been conducted at an unscheduled visit, if necessary. These participants were required to arrive at the clinic prior to taking their morning dose of LCM. Participants were administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) could be performed 30 minutes to 1 hour after administration of LCM (ie, at LCM steady state C_{max}). A list of SAEs was included in this amendment in compliance with recent US FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug Application.</p> |

| | |
|------------------|---|
| 09 April 2012 | <p>Selected sites were permitted to directly enroll in SP848 up to approximately 100 eligible pediatric study participants ≥ 4 to ≤ 17 years of age with POS (deemed appropriate for treatment with adjunctive LCM) who had not previously participated in a LCM clinical study. The purpose of enrolling these study participants directly into SP848 was to obtain sufficient long-term safety exposures in the age range of ≥ 4 to ≤ 17 years of age; the additional long-term safety data were to be included in planned regulatory submissions for LCM as adjunctive therapy for POS in pediatric study participants aged 4 years and above with epilepsy. Based on regulatory agency recommendations to include scales to measure development and cognition, the Achenbach Child Behavior Checklist (CBCL); Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley®-III); and Tanner Scale were selected by UCB and added as assessments in SP848. In addition, a LCM palatability and ease of use questionnaire was added to the study assessments.</p> |
| 22 January 2013 | <p>In the FDA Division of Neurology Products' 06 Aug 2012 Request for Information regarding SP847 Protocol Amendment 5, the Agency recommended that UCB revise an inclusion criterion to require the use of more than 1 AED as monotherapy before initiating adjunctive LCM therapy in SP847. UCB made this recommended change in the SP847 protocol (Amendment 6). In alignment with SP847, Inclusion Criterion 7 was modified to require that each study participant in SP848 have had uncontrolled POS after an adequate course of treatment (in the opinion of the investigator) with at least 2 AEDs (concurrently or sequentially). Inclusion Criterion 7 applied only to study participants who enrolled directly into SP848 without previous participation in a LCM clinical study. The Behavior Rating Inventory of Executive Function® (BRIEF®)/Behavior Rating Inventory of Executive Function®-Preschool Version (BRIEF®-P), Pediatric Quality of Life Inventory (PedsQL™), and health care resource use were added as assessments in SP848.</p> |
| 16 November 2016 | <p>The primary purpose of this protocol amendment was to permit enrollment of up to approximately 75 eligible pediatric study participants ≥ 4 to < 17 years of age with POS (deemed appropriate for treatment with LCM) who had previously participated in the iv LCM clinical study EP0060. The purpose of enrolling these study participants was to obtain additional long-term safety exposures in the age range of ≥ 4 to < 17 years of age; the additional long-term safety data were submitted on 30 Apr 2020 and 15 May 2020 to the LCM iv and tablet New Drug Applications, respectively. Of note, EP0060 was further amended (Protocol Amendment 3; 30 Apr 2018) to allow enrollment of up to 100 study participants ≥ 1 month to < 17 years of age, all of whom could rollover into SP848. Sponsor language for monitoring of PDILI events was added to increase clarity for the sites and to align across programs. Addition of this language was to align with FDA guidance regarding monitoring of PDILI events and did not reflect a change in the liver safety signal for LCM. In addition, Exclusion Criterion 16, which excluded use of vigabatrin or felbamate, was removed.</p> |
| 06 February 2017 | <p>This administrative amendment fixed the numbering of the exclusion criteria that resulted from the removal of Exclusion Criterion 16 in Protocol Amendment 6.</p> |
| 20 October 2020 | <p>The primary purpose of this protocol amendment was to align with modifications made to the Paediatric Investigation Plan. Changes included:</p> <ul style="list-style-type: none"> • A new categorization for main primary and secondary endpoints key binding element was proposed to ensure reporting compliance with registries (European Union Drug Regulating Authorities Clinical Trials Database, clinicaltrials.gov). This categorization did not affect the type or processing of data collected and reported in the study report, which were assessed as initially planned. • Further clarification was provided for the study duration as well as the wording and categorization of the primary, secondary, and other variables. In addition, language specifying applicable study conduct modifications due to the coronavirus disease 2019 (COVID-19) pandemic was added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported