



## Clinical trial results:

**An open-label pilot study to assess the safety of oral lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004379-22 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 30 August 2011 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 30 June 2016 |
| First version publication date | 27 June 2015 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | SP0961 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01118949 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | UCB BIOSCIENCES, INC.   |
| Sponsor organisation address | 8010 Arco Corporate Drive, Raleigh, United States, 27617  |
| Public contact               | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |
| Scientific contact           | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |

Notes:

### Paediatric regulatory details

|  |     |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| 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                       | 11 November 2011 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 August 2011   |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety of Lacosamide (LCM) in subjects with uncontrolled primary generalized tonic-clonic (PGTC) seizures with idiopathic generalized epilepsy (IGE).

Protection of trial subjects:

No specific measures in the protocol to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 17 May 2010 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 14 Months   |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 49 |
| Worldwide total number of subjects   | 49                |
| EEA total number of subjects         | 0                 |

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)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 3  |
| Adults (18-64 years)                      | 46 |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Safety Set (SS) includes all enrolled subjects who took at least 1 dose of Lacosamide (LCM).

### Pre-assignment

Screening details:

Participant Flow and Baseline Characteristics refer to the Safety Set (SS).

### 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 |
|-----------|------------|

Arm description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

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

Dosage and administration details:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

| Number of subjects in period 1 | Lacosamide |
|--------------------------------|------------|
| Started                        | 49         |
| Completed                      | 40         |
| Not completed                  | 9          |
| Consent withdrawn by subject   | 4          |
| Non-Fatal, Serious AE(s)       | 1          |
| Non-Fatal, Non-Serious AE(s)   | 4          |



## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Lacosamide |
|-----------------------|------------|

Reporting group description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

| Reporting group values  | Lacosamide | Total |  |
|-------------------------|------------|-------|--|
| Number of subjects      | 49         | 49    |  |
| Age Categorical         |            |       |  |
| Units: Subjects         |            |       |  |
| <=18 years              | 4          | 4     |  |
| Between 18 and 65 years | 45         | 45    |  |
| >=65 years              | 0          | 0     |  |
| Age Continuous          |            |       |  |
| Units: years            |            |       |  |
| arithmetic mean         | 29.7       |       |  |
| standard deviation      | ± 10.1     | -     |  |
| Gender Categorical      |            |       |  |
| Units: Subjects         |            |       |  |
| Female                  | 36         | 36    |  |
| Male                    | 13         | 13    |  |
| Height                  |            |       |  |
| Units: centimeter (cm)  |            |       |  |
| arithmetic mean         | 168.08     |       |  |
| standard deviation      | ± 9.32     | -     |  |
| Weight                  |            |       |  |
| Units: kilogram (kg)    |            |       |  |
| arithmetic mean         | 77.9       |       |  |
| standard deviation      | ± 19.8     | -     |  |

## End points

### End points reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Lacosamide |
|-----------------------|------------|

Reporting group description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

### Primary: Change in the number of seizure days with absence seizures from the Baseline Phase to the Maintenance Phase

|                 |  |
|-----------------|--|
| End point title | Change in the number of seizure days with absence seizures from the Baseline Phase to the Maintenance Phase <sup>[1]</sup> |
|-----------------|--|

End point description:

During the study subjects kept a diary to record daily seizure activity from Visit 1 until the end of study participation. The following information has been recorded:

- Seizure type
- Seizure frequency

A negative value in change of seizure days with absence seizures shows a decrease in seizure days with absence seizures.

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

End point timeframe:

From Baseline Phase (Weeks 0 to 4) to Maintenance Phase (Weeks 8 to 13)

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 study. Results were summarized in tables as descriptive statistics only.

| End point values                     | Lacosamide      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 44              |  |  |  |
| Units: number of seizure days        |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| mean (standard deviation)            | -0.37 (± 4.8)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in the number of seizure days with myoclonic seizures from the Baseline Phase to the Maintenance Phase

|                 |  |
|-----------------|--|
| End point title | Change in the number of seizure days with myoclonic seizures from the Baseline Phase to the Maintenance Phase <sup>[2]</sup> |
|-----------------|--|

---

**End point description:**

During the study subjects kept a diary to record daily seizure activity from Visit 1 until the end of study participation. The following information has been recorded:

- Seizure type
- Seizure frequency

A negative value in change of seizure days with myoclonic seizures shows a decrease in seizure days with myoclonic seizures.

---

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

---

**End point timeframe:**

From Baseline Phase (Weeks 0 to 4) to Maintenance Phase (Weeks 8 to 13)

---

**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 study. Results were summarized in tables as descriptive statistics only.

| End point values                     | Lacosamide         |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 44                 |  |  |  |
| Units: number of seizure days        |                    |  |  |  |
| arithmetic mean (standard deviation) |                    |  |  |  |
| mean (standard deviation)            | -2.19 ( $\pm$ 5.8) |  |  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

---

---

**Secondary: Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)**

---

|                 |   |
|-----------------|---|
| End point title | Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase) |
|-----------------|---|

---

**End point description:**

Subjects were asked to return to the clinic on the morning of the day prior to Visit 2 and Visit 6 to begin 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. Only subjects with an evaluable EEG measurement with > 19 interpretable hours at Visit 2 and Visit 6 are included in this analysis. The general spike-wave discharges are calculated per interpretable hours.

---

---

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

---

**End point timeframe:**

From Visit 2 (Week 4) to Visit 6 (Week 8)

---

| End point values                     | Lacosamide           |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Reporting group      |  |  |  |
| Number of subjects analysed          | 40                   |  |  |  |
| Units: 1/hour                        |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| mean (standard deviation)            | -3.47 ( $\pm$ 55.85) |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in count of 3 Hertz (Hz) spike-wave discharges (during waking hours) on 24-hour ambulatory Electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)

|                 |  |
|-----------------|--|
| End point title | Changes in count of 3 Hertz (Hz) spike-wave discharges (during waking hours) on 24-hour ambulatory Electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase) |
|-----------------|--|

#### End point description:

Subjects were asked to return to the clinic on the morning of the day prior to Visit 2 and Visit 6 to begin 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. Only subjects with an evaluable EEG measurement with > 19 interpretable hours at Visit 2 and Visit 6 are included in this analysis. The 3 Hertz (Hz) spike-wave discharges are calculated per awake hours.

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

#### End point timeframe:

From Visit 2 (Week 4) to Visit 6 (Week 8)

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Lacosamide      |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 40              |  |  |  |
| Units: 1/hour                        |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| mean (standard deviation)            | 0.13 (± 2.17)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with treatment emergent adverse events (TEAEs) during the 10-week Treatment Period

|                 |   |
|-----------------|---|
| End point title | Number of subjects with treatment emergent adverse events (TEAEs) during the 10-week Treatment Period |
|-----------------|---|

#### End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

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

#### End point timeframe:

From Visit 2 (Week 4) to Visit 7 (Week 13)

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Lacosamide      |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 49              |  |  |  |
| Units: participants         |                 |  |  |  |
| TEAEs                       | 43              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects withdrawn from the study due to Treatment Emergent Adverse Events (TEAEs) during the 10-week Treatment Period

|                 |  |
|-----------------|--|
| End point title | Number of subjects withdrawn from the study due to Treatment Emergent Adverse Events (TEAEs) during the 10-week Treatment Period |
|-----------------|--|

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

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

End point timeframe:

From Visit 2 (Week 4) to Visit 7 (Week 13)

|                                |                 |  |  |  |
|--------------------------------|-----------------|--|--|--|
| <b>End point values</b>        | Lacosamide      |  |  |  |
| Subject group type             | Reporting group |  |  |  |
| Number of subjects analysed    | 49              |  |  |  |
| Units: participants            |                 |  |  |  |
| Subject Withdrawal due to TEAE | 5               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected up to 16 weeks from Baseline (Week 0 - Week 4) over the 3-weeks Titration Period (Week 4 - Week 7) and the 6-weeks Maintenance Period (Week 7 - Week 13) to the Final Clinic Visit at the end of Week 16.

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS). SS includes all enrolled subjects who received at least one dose of Lacosamide.

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Lacosamide |
|-----------------------|------------|

Reporting group description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

| Serious adverse events                            | Lacosamide     |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 1 / 49 (2.04%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Nervous system disorders                          |                |  |  |
| Petit mal epilepsy                                |                |  |  |
| subjects affected / exposed                       | 1 / 49 (2.04%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |

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

| Non-serious adverse events                            | Lacosamide       |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 39 / 49 (79.59%) |  |  |
| Injury, poisoning and procedural complications        |                  |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Contusion<br>subjects affected / exposed<br>occurrences (all)          | 3 / 49 (6.12%)<br>4    |  |  |
| Nervous system disorders   |                        |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)          | 19 / 49 (38.78%)<br>27 |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)           | 8 / 49 (16.33%)<br>8   |  |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)         | 8 / 49 (16.33%)<br>8   |  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)             | 6 / 49 (12.24%)<br>8   |  |  |
| Migraine<br>subjects affected / exposed<br>occurrences (all)           | 4 / 49 (8.16%)<br>4    |  |  |
| Petit mal epilepsy<br>subjects affected / exposed<br>occurrences (all) | 4 / 49 (8.16%)<br>4    |  |  |
| General disorders and administration<br>site conditions                |                        |  |  |
| Gait Disturbance<br>subjects affected / exposed<br>occurrences (all)   | 5 / 49 (10.20%)<br>5   |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)            | 6 / 49 (12.24%)<br>6   |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)             | 4 / 49 (8.16%)<br>5    |  |  |
| Eye disorders  |                        |  |  |
| Diplopia<br>subjects affected / exposed<br>occurrences (all)           | 4 / 49 (8.16%)<br>4    |  |  |

|  |  |  |  |
|--|--|--|--|
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 13 / 49 (26.53%)<br><br>15<br><br>7 / 49 (14.29%)<br><br>9 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnea<br>subjects affected / exposed<br>occurrences (all)   | 4 / 49 (8.16%)<br><br>4                                    |  |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 3 / 49 (6.12%)<br><br>3                                    |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 49 (12.24%)<br><br>6                                   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 02 November 2010 | <p>The original protocol, dated 31 Aug 2009, was amended on 02 Nov 2010; changes are described in the following subsection.</p> <p>Protocol Amendment 1</p> <p>Changes based on the amendment that affected SP0961 included, but were not limited to:</p> <ul style="list-style-type: none"><li>• Administrative changes included changes to the Sponsor Authorization and Study Contact Information for the Clinical Program Director and Clinical Trial Biostatistician</li><li>• Increased the number of study sites from 10 to 25</li><li>• Revised the inclusion criterion for number of PGTC seizures prior to Baseline to increase the duration from 28 days to 12 weeks</li><li>• Removed the inclusion criterion for number of PGTC seizures during the Baseline Phase</li><li>• Added an exclusion criterion for known sodium channelopathy, such as Brugada syndrome</li><li>• Revised withdrawal criteria and follow-up recommendations for abnormal liver function tests (LFTs)</li><li>• The primary variable of percent change in PGTC seizure frequency per 28 days from Baseline Phase to the Maintenance Phase was removed</li><li>• Clarified that the secondary variable for count of 3Hz SW discharges on 24-hour ambulatory EEG only applied to waking hours</li><li>• The term "Holter monitor" was replaced by "recording device" for the 24-hour ambulatory EEG recordings</li><li>• Urinalysis parameter acetone was changed to ketones</li><li>• "Procedures for Data Monitoring Committee" was replaced by "DMC Charter"</li></ul> <p>Based on the date of the amendment, 9 subjects were enrolled in the study prior to this amendment</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported